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COLLATERAL CIRCULATION, NATURAL AND ARTIFICIAL

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The custom of establishing memorial lectureships in honor of those distinguished in science and in the arts is an old one that is common to many countries. To my mind, it is a wholly admirable way of paying tribute to those who have left us in their debt. The narrow view is sometimes expressed that in the course of time subjects will tend to elude lecturers, but this will happen only if the lectures are restricted in scope. The regulations framed by the Board of Regents of the American College of Surgeons are generous enough to admit any topic relating to the life and to the work of its distinguished founder—"a scientific subject"—a definition that might well have been Martin's own.

I am very conscious of the honor you have done me in asking me to deliver this Martin lecture, and I tender my thanks to you, Mr. Chairman, and to the Regents. You will perhaps forgive me if I find particular pleasure in that provision of the Regents which associates with Franklin H. Martin, Isabelle Hollister Martin, his wife.

I hope that Martin would have approved of my choice of subject—"Collateral Circulation, Natural and Artificial"; at any rate he had a habit of working from first principles. Indeed I chose the subject from among my own interests because I knew that he had devoted considerable thought to it. He would not have devised and practiced his operation of transvaginal ligature of the uterine arteries for excessive bleeding, unless he had been certain that the uterus had a collateral circulation sufficient to maintain its nutrition; and he was to learn by experience that the very richness of this collateral circulation occasionally defeated his ingenious idea.

I quote his analysis of this aspect of his problem from his original paper, published in the *American Journal of Obstetrics* in April, 1893.

> "The first objection which arose in my mind was the fact that there was such intimate anastomosis between the uterine artery and the spermatic or ovarian artery above, that a compensatory supply of blood would soon be derived from that source.
>
> "I met that objection, mentally, with the fact (a) that the compensatory supply of blood must come from a much smaller artery which derives its blood in a single channel from a long distance; (b) that the nerve supply to the trunks of the two arteries were comparatively widely separated, and that by the time the nervous mechanism had communicated the fact of the blood drought in the uterus and had succeeded in beginning the process of correcting it, the abnormal growth would have been changed in nutrition, atrophy would have begun, and in the meantime blood would have been saved.
>
> "The second objection which presented itself to me was the fact that I might not be able to ligate the main artery far enough away from the uterus to prevent collateral circulation being derived from branches given off further back. As collateral circulation is oftenest supplied by arteries arising from the same source or trunk back of the obstruction, this gave me more anxiety than my first objection. Fortunately there were two methods of avoiding the difficulty—viz. (a) by being able to ligate the trunk of the uterine artery far enough away from the uterus to include its uterine branch; and (b) by ligating not only the uterine artery, but by including *en masse* the whole base of the broad ligament, thereby shutting off all possibility of leaving any anomalous branches, should they exist."

FROM time to time every surgeon, whether he be a general surgeon or a specialist, is confronted with the problem of conserving some tissue, or some organ, whose normal arterial supply has been interrupted by injury, by disease, or by design. I do not underestimate the importance in such circumstances of adequate venous and adequate lymphatic drainage; but my time is limited and fortunately Nature has been more prodigal in the provision of alternative venous and lymphatic routes than she has been in arranging for arterial collaterals, to which I shall confine my attention.

It will be wise for me to follow an excellent rule in the consideration of any scientific

Regius Professor of Clinical Surgery and Professor of Surgery in the University of Edinburgh.

The fourth Martin Memorial Lecture, presented before the Clinical Congress of the American College of Surgeons, Chicago, October 17 to 21, 1949.

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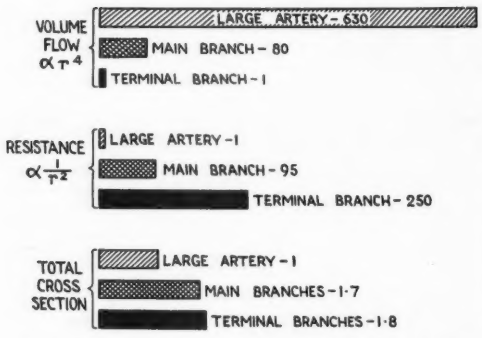

Fig. 1. Volume flow, internal resistance, and total cross-section of large arteries, main branches, and terminal branches.

problem: that is, to begin by defining it. Reduced to its essentials, the problem is to maintain a sufficient flow of blood through the capillaries of the threatened part to suffice for its nutrition when it is at rest, and to encourage the increase of this flow to suffice for its nutrition when it is physiologically active. This is a problem which can be stated in plain terms, for the flow of blood through any given capillary can be expressed according to Poiseuille's law:

$$\text{Quantity of blood varies with } \frac{(P_1 - P_2)\, r^4}{L}$$

where P_1 is the blood pressure at the arteriolar end of the capillary loop, P_2 the blood pressure at the venous end of the loop, r the radius of the capillary, and L its length. Obviously the most important value is r: for if the radius of the capillary is doubled, the flow within it is increased sixteenfold. It is an intriguing thought that at any given time only about 6 per cent of the total blood volume is accommodated in the capillaries: 94 per cent of the blood volume is either approaching them or returning from them. It is with the moiety which is approaching them that we are specially concerned.

We can now define our therapeutic objective: it is, to keep the pressure at the arterial end of the capillary as high as possible, and so to keep its caliber as wide as possible. To do this, in clinical practice we must first arrange for two quite fundamental requisites: (1) we must maintain adequate blood volume, and (2) we must maintain normal or near normal systemic arterial pressure, that is, one which is not being maintained by excessive vasoconstriction to compensate for loss of circulating blood.

The clinical answer to these first demands —if one is necessary—is early and adequate transfusion. Given this, what alternative pathways are available to bring blood to parts threatened by ischemia? We may adopt Mall's classification, and decide that they are large arteries, their main branches, their terminal branches and their arterioles. Moreover, in the majority of cases the blocks with which we are concerned affect large arteries, and so we may concentrate attention upon their main and terminal branches, and upon the arterioles. In order to define our problem more accurately, we must study, for each of these types of vessel, three properties: (1) the volume flow, (2) the internal resistance, and (3) the total cross-sectional area.

As we have seen, the volume of blood passing a given point in an artery varies with the fourth power of its radius (Fig. 1). This factor is so important that after the interruption of a large artery the surgeon must do everything he can to secure routes of large caliber. On this physical law was based the use of silver tubes in the war of 1914 to 1918, and its variants in the last war—glass tubes and immediate homografts of veins—to replace an obstructed arterial segment or to bridge a missing one. Substitutions of such large caliber permit maximum flow, with minimum resistance. In the absence of such substitutes for arterial segments, we must depend upon the main and terminal branches of arteries. At once difficulties increase, for the volume flow in channels of this smaller size is much reduced, and the internal resistance is increased. Moreover, their total cross-sectional area is not increased sufficiently to offset these disadvantages (Fig. 1). Also in these vessels volume flow may be reduced and internal resistance increased by the presence of spasm. We must therefore direct clinical treatment to maintaining as wide a caliber as possible in them. This leads me to state a consideration which is of great value in prognosis. If we examine the architectures

Fig. 2. Arteriogram showing blood returned to popliteal artery beyond a block.

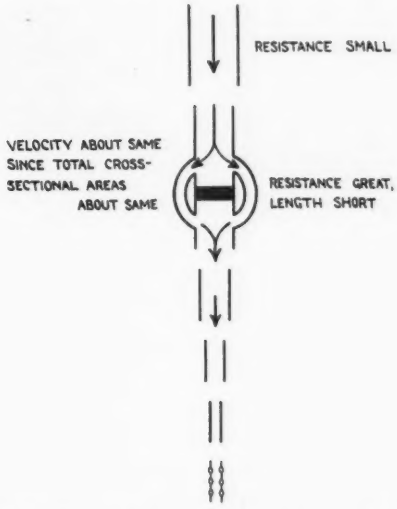

Fig. 3. Physics of collateral circulation shown in Figure 2. Blood returned to main channel and reaches capillary with little increase in loss of pressure, because length of narrow vessels is short. This means well filled capillaries.

of collateral circulations, we shall find that they fall into two well defined groups. In the first group, after a short course in alternative channels, the arterial blood is returned into the main artery or arteries of the part (Fig. 2). There is little loss of volume flow and little loss of blood pressure in overcoming internal resistance in the alternative channels because they are short.[1] Blood reaches the arterioles in quantity and at a high pressure (Fig. 3). In such cases, the prognosis for the nutrition of the threatened part is good, whether it be the distal part of a limb, or the gut; and the clinical indication of this desirable state of affairs is the immediate or early presence of arterial pulsation distal to the obstructed artery. The pulse returns only when large and short collateral channels are available, when collateral channels are small, the pulse is dissipated, and the considerable differences in their lengths would lead to the arrival at the periphery of a multitude of tiny impulses so out of phase with each other that they would cancel each other out.

[1]In one of my cases, after ligature of the brachial artery in the antecubital fossa, the blood pressure in the forearm fell from 118/76 to 102/68.

In the second group, the arterial blood never returns to the main arteries, usually because they have been blocked by extensive thrombosis. The part depends for its nutrition solely upon main and terminal branches (Fig. 4). Because of the progressive narrowing of these branches as they approach the periphery, there is great loss of volume flow, and much loss of blood pressure in overcoming their internal resistance (Fig. 5). Blood reaches the arterioles in reduced quantity and at a low pressure. In such cases, the prognosis for the nutrition of the threatened part is bad, whatever its situation; and the clinical indication of this ominous state of affairs is the absence of arterial pulsation detectable either by the finger or by a more sensitive instrument such as an oscillometer.

We have now followed the arterial supply to the arterioles. In a normal arterial tree this stage is reached after the expenditure of arterial pressure of about 20 millimeters of mercury in overcoming internal resistance (Fig. 6); when short collateral vessels return the blood to main channels the loss of pressure is but little more, but when small branches alone are available the loss of pres-

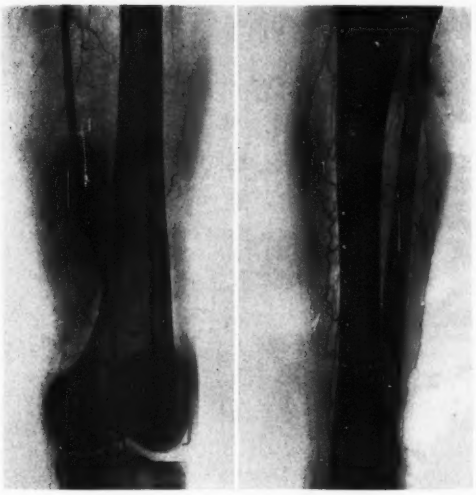

Fig. 4. Arteriogram showing blood reaching periphery beyond a block, through terminal branches only.

sure is considerable. Passage of the blood through the arterioles absorbs much more of its energy; in a normal circulation the fall in pressure thus produced is of the order of 60 millimeters of mercury. This is because the internal resistance in an arteriole is about a thousand times that in an average terminal branch, whereas the total cross-sectional area of the arterioles is only about twenty-five times that of the terminal branches. Landis has shown that the average pressure at the

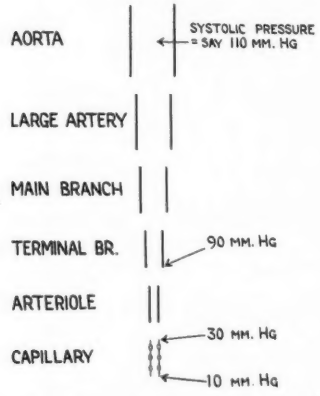

Fig. 6. Normal distribution of blood pressure from aorta to venous end of capillary.

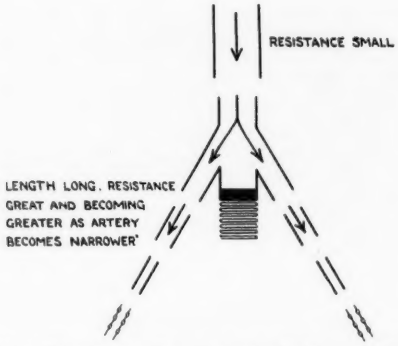

Fig. 5. Physics of collateral circulation shown in Figure 4. Blood reaches capillary only through alternative small arteries, with much loss of pressure since these vessels are narrow, and longer because tortuous. This means poorly filled capillaries.

arteriolar end of a capillary loop is 32 millimeters of mercury.

Although the total cross-sectional area of the capillaries is large, the rate of blood flow is so slow that relatively little energy is required to drive blood through them. At the venous end of a capillary loop the average pressure is 12 millimeters of mercury, so that the fall in pressure in the loop is 20 millimeters of mercury. Thus the amount of energy expended in driving blood through the capillaries is of the order of that expended in driving blood from the aorta to the end of the arterial terminal branches.

It is clear, from a consideration of these data, that in order to avoid, to diminish, or to correct ischemia the clinician must try to arrange: (1) that as much blood as possible reaches the arterioles, by keeping the arterial main and terminal branches dilated, and (2) that the arterioles are kept widely dilated, to increase the amount of blood reaching the capillaries.

The remainder of this paper will describe various methods for accomplishing this.

GENERAL METHODS

When arterial obstruction is of slow evolution, enlargement of pre-existing collateral channels may keep pace with the gradual narrowing of the original channel, provided that the needs of the tissues are not increased by increased calls upon their physiological ac-

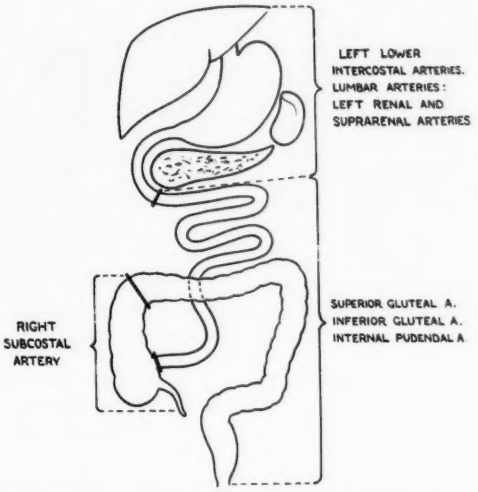

Fig. 7. Chiene's case. Diagram to show blood supply of alimentary tract by collateral arteries.

tivity. The most remarkable example of such a natural adjustment of which I have knowledge was recorded in 1869 by John Chiene, one of my predecessors in Edinburgh. The origins of the celiac, superior mesenteric, and inferior mesenteric arteries, and the lower part of the abdominal aorta had all undergone gradual obliteration. The supply of all the viscera was maintained by somatic arteries and by the subperitoneal arterial plexus (Fig. 7).

The majority of you will have encountered less extensive adjustments of this type. If the existence of a block is detected clinically, it is well to prevent consecutive thrombosis by the administration of anticoagulant drugs. In an emergency, such as the lodgment of an embolus, or the sudden closure of an arteriosclerotic artery by thrombus, heparin will be necessary at first, until coagulation can be controlled by a drug effective by mouth—dicumarol, or better its successors tromexan and pelentan. If the process is less rapid one of the latter three drugs is all that is necessary. Even in emergency, with this precaution the collateral channels are usually sufficient for nutrition, and it is fascinating to follow their effectiveness by clinical methods (Fig. 8).

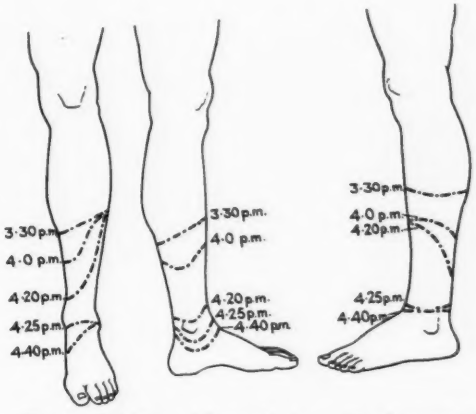

Fig. 8. Embolism of femoral artery. Development of collateral circulation indicated by recession of analgesia. Patient A. B., February 25, 1948.

General measures include rest, which reduces the metabolic needs of the part, and the avoidance of local heating, which increases them.

NONOPERATIVE METHODS FOR DILATING ARTERIAL BRANCHES

The nonoperative methods for dilating arterial branches fall into two groups. First, peripheral vasodilatation may be produced reflexly by heating areas of the body other

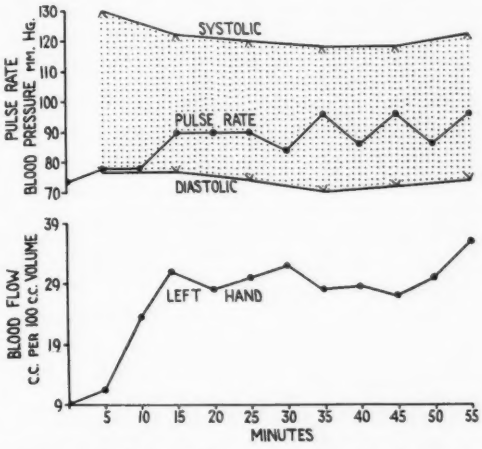

Fig. 9. Reflex vasodilatation, produced by immersing legs in water at 45 degrees C. To show small fall in blood pressure but increase in pulse rate associated with full vasodilatation in left hand.

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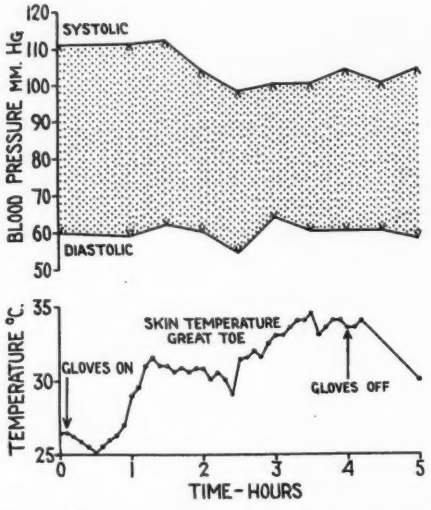

Fig. 10. Reflex vasodilatation, produced by warming hands in electrically heated gloves. To show small effect on blood pressure associated with considerable but not full vasodilatation.

than the threatened part at a temperature of about 45 degrees C.; and second, it may be induced by the action of drugs. Both these methods have the disadvantage that widespread vasodilatation leads to a fall in peripheral resistance and so to a fall in aortic blood pressure, which is undesirable because it must be compensated for by increase in cardiac output by increase in pulse rate, if peripheral volume flow is to be maintained at a high level. This disadvantage is least if the vasodilatation is induced reflexly, when the fall in blood pressure is slight (Fig. 9).

To secure the best results in treatment I believe that it is absolutely essential for the vasodilatation to be *continuous and prolonged;* it is difficult if not impossible to achieve this by the action of drugs. We have found that peripheral vasodilatation may be continuously maintained, with least inconvenience to the patient, by the use of electrically heated gloves. The silk inner-gloves used in military aeroplanes are best, because they need not be removed while the patient is writing or reading; a small pad of chamois leather sewn to the palmar surface of the tip of the index finger makes it easy for the patient to turn

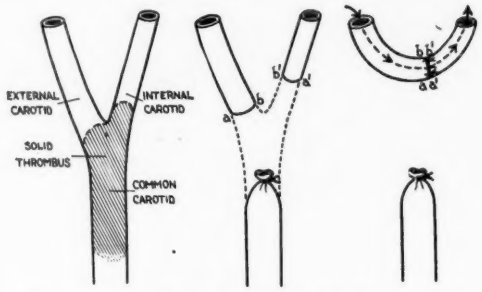

Fig. 11. Method of restoring arterial circulation after resection of bifurcation of common carotid artery.

pages. By this method vasodilatation may be kept up all day (Fig. 10). It need not be artificially produced during sleep, because then the vessels are relaxed.

Peripheral vasodilatation may be produced by drugs in several different pharmacological ways. First, the action of the drug may be central, and cause a general decrease in vascular tone; this is one action of the dihydrogenated alkaloids of the dimethylpyruvic acid group, the mixture of which is called hydergine (Sandoz). Second, vasoconstrictor impulses may be blocked at their synapses in sympathetic ganglia, as by tetraethyl ammonium bromide or chloride and by C5 and C6, or at the periphery in the neuromuscular junctions in the walls of the arteries, as by the second action of hydergine. Third, vasodilator nerves may be stimulated as by butylsympatol, which like hydergine acts at the periphery. We have tested these drugs and many others on a number of patients, with the following results:

Hydergine. We have found this to produce (a) slight fall in blood pressure, (b) no change in pulse rate, (c) slight increase in blood flow through subcutaneous vessels, and (d) variable changes in blood flow through muscles. We do not feel that it is of value in the type of case I have been discussing, although in certain other fields it is promising.

Pentamethonium iodide (C5) and hexamethonium iodide (C6).[1] Our investigation of these drugs showed that they produced: (a) a moderate fall in blood pressure; (b) little change in the pulse rate; (c) a rapid and prolonged increase in the blood flow through the subcu-

[1] Burt, Catherine, and Graham, A. J. P. Brit. M. J., 1950, 1:455.

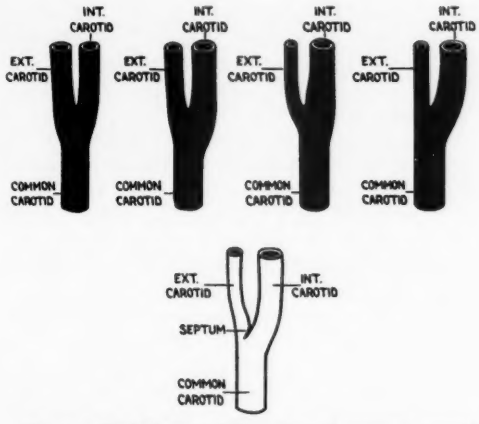

Fig. 12. Variations at bifurcation of common carotid artery, and intra-arterial septum.

taneous vessels of the lower limbs but no significant increase in the upper limbs; and (d) little change in the blood flow through muscles. We feel that these drugs are unlikely to be useful in securing vasodilatation in the upper limb but may be of considerable value in securing vasodilatation in the lower limb.

Butylsympatol. In our tests this drug has produced: (a) a rise in systolic blood pressure, and a slight fall in diastolic blood pressure, (b) no increase in pulse rate, (c) variable changes in blood flow through subcutaneous vessels, and (d) in 50 per cent of cases, an increase in blood flow through muscles. We feel that butylsympatol may have a place in the treatment of threatened ischemia, particularly in improving the blood supply to muscles.

Although drugs may ensure transient increases of peripheral blood flow greater than that resulting from reflex vasodilatation produced by heating indifferent parts, I believe that this is offset by the effect of the *continuous* mild vasodilatation produced by the latter treatment, which is also infinitely more comfortable for the patient.

OPERATIVE MEASURES

I shall not refer to the correction of intrathoracic anomalies, so ably described by the Martin lecturer of 1948, Dr. Crafoord. I have already referred to the introduction of free

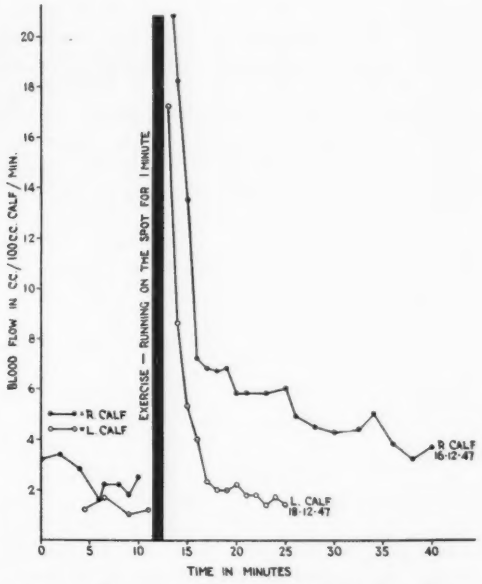

Fig. 13. To show that the flow of blood in the calf muscles after exercise is not altered after sympathectomy. Patient Lieutenant W. K. Responses to exercise 3 months after right lumbar sympathectomy. The tests were done on different days and the results are therefore not exactly quantitatively comparable but there is a similar increase in both legs immediately following exercise. Sympathectomy does not affect the response of muscle blood vessels to chemical stimuli.

venous or arterial grafts. There is also a procedure which I have used in one region which utilizes a collateral circulation to return blood to a major vessel of large caliber. It is applicable to other regions.

When the bifurcation of the common carotid artery is obstructed by thrombus, or when it is necessary to resect it in dealing with a tumor, it may be possible to utilize the rich anastomoses between the two external carotid arteries to return blood to the internal carotid. The development of these anastomoses is encouraged, when this is necessary, by performing a preliminary cervical sympathectomy on the normal side. After the common carotid has been ligatured and the bifurcation resected, the uninvolved parts of the external carotid and internal carotid are controlled by clamps, and the ends of the two vessels are united by suture (Fig. 11); in such a case I have seen pulsation transmitted to the internal carotid.

When a procedure is a success, it is always a salutary and often a chastening experience

to make a detailed examination of its possibilities. My colleague in anatomy, Professor Brash, found such considerable variations in the size of the internal and external carotids, that their union by suture might not be always practicable (Fig. 12). Moreover we were made aware of a potential barrier to the collateral circulation after ligature of the common carotid, in the presence of an intra-arterial septum at the bifurcation, which might be as much as 12 millimeters long.

Lastly there is the operation of sympathectomy, which includes division of the vasoconstrictor nerves destined for the precarious region of the body. This procedure is based on sound physiological principles. The area in which constrictor tonus is released is a limited one. Over the remainder of the body constrictor tonus maintains the peripheral resistance at normal values, with the result that the blood pressure is maintained at its normal value. As we have seen, this and the maintenance of normal blood volume must be the first cares of the surgeon. The only contraindication to the operation is the existence of organic disease in the arterial tree of the threatened part, which deprives the vessels of their capacity to dilate and may even convert them into rigid tubes. Its immediate postoperative result is to supplement the natural resources of the body against the threat of ischemia at the time when aid is most valuable, for the nutritional fate of ischemic parts is rapidly settled, and ischemic pathological changes are largely irreversible. The objection that after sympathectomy blood is deflected from muscles to subcutaneous vessels does not withstand investigation (Fig. 13). Its remote result is to retain for the area a most valuable proportion of the immediate postoperative increase in blood flow, assessed with due regard to the age of the patient and to the pathological nature of the original obstructing lesion.

And so I come to the end of my lecture. In surgery, as in any other science, it is wise to resist temptation to oversimplify any problem, however easy its solution may appear at first sight. I chose this problem, with the approval of the then chairman of the Board of Regents, nearly two years ago, because I thought it would have intrigued Franklin H. Martin. But the particular problem to be investigated is a secondary matter. The method of approach is inviolable, and my acquaintance with American surgeons and with American surgical literature leads me to hope that you will have been sympathetic to mine.

SUMMARY

1. The physics of the arterial circulation before and after obstruction of a main artery is described.

2. The task of a collateral circulation is to carry blood to the capillaries in quantity and at a high pressure.

3. This is best accomplished when the alternative routes return blood to the main arteries distal to a block.

4. General measures to encourage collateral circulation include rest, anticoagulant drugs, and avoidance of local heat to the ischemic part.

5. The collateral circulation may be encouraged artificially by reflex vasodilatation, by drugs, or by operation. The advantages and disadvantages of each of these methods are discussed.

AN END RESULT STUDY OF INTRACAPSULAR FRACTURE OF THE NECK OF THE FEMUR

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New York, New York

THE intracapsular fracture of the femoral neck, in spite of all the improvements in treatment during the past 20 years, remains a serious problem with several perplexing and as yet unsolved complications. Our experience with this fracture over a period of 18 years affords a record of gratifying accomplishment with greatly improved end results. We are still confronted with nonunion and with circulatory disturbance in united fractures, though fortunately in diminishing numbers and percentage.

The average age of our patients throughout the years has been 65 years and nearly 80 per cent of them are women. Since these patients sustain their fractures at the upper limit of life expectancy, long follow-up studies are not readily nor frequently presented. We have gained the impression that many surgeons know little or nothing of their patients' final results after the first few months.

Many technical procedures and prosthetic devices to secure internal fixation of these fractures have been advocated without a sufficiently adequate follow-up study to justify their use. The unwary or inexperienced surgeon is beset with many pitfalls if he believes all that he hears or reads.

The internal fixative agent that we have found effective, is the three-flanged nail presented by Smith-Petersen. We have adhered to this nail from the beginning of our operative treatment of these fractures. Unfortunately we had to learn by experience that the open reduction of the fracture originally recommended by Smith-Petersen resulted, in our hands, in an extremely high incidence of serious vascular disturbance in the femoral head.

From the Orthopaedic Service at St. Luke's Hospital.
Presented before the Clinical Congress of the American College of Surgeons, Chicago, October 17 to 21, 1949.

FOLLOW-UP STUDY

This follow-up study over the 18 year period from 1930 to 1948 is, we believe, in some ways unique. We know the final outcome in 225 of our 235 patients, a 95.7 per cent follow-up. We have followed the survivors for an average of over 30 months after the fracture, and in 48 patients we have made a follow-up study of from 3 to 10 years. This is a complete analysis of our series of intracapsular fractures of the femur, aside from the 10 patients who were lost to followup during the 18 years.

The study covers three series of cases, the first two previously reported (2, 3), each representing an era in our attempt to grapple with the problems which this fracture presents.

1. *The nonoperative period, 1930 to 1935* (3). Fifty fractures of the neck of the femur treated by plaster of paris spica, traction, or sand bags were analyzed. At this time we learned that the undisplaced intracapsular fracture invariably united uneventfully if it was protected and not meddled with. We also learned that displaced intracapsular fractures requiring manipulative reduction, "*immobilized*" by plaster of paris spica, united in only 23.6 per cent of the cases.

2. *Early operative period, 1936 to 1940* (2). A series of 60 cases represent this change-over period when we abandoned plaster of paris and adopted reduction and internal fixation of the fracture. In the first 14 of these patients with displaced fractures, open reduction and fixation with the three-flanged nail was attempted. Union of the fracture ensued in 50 per cent of these 14 patients *but* in 42 per cent of those fractures which united marked symptomatic circulatory disturbance developed in the femoral head (Fig. 1). This form of treatment was so obviously fraught with danger to the circulation of the femoral head that we

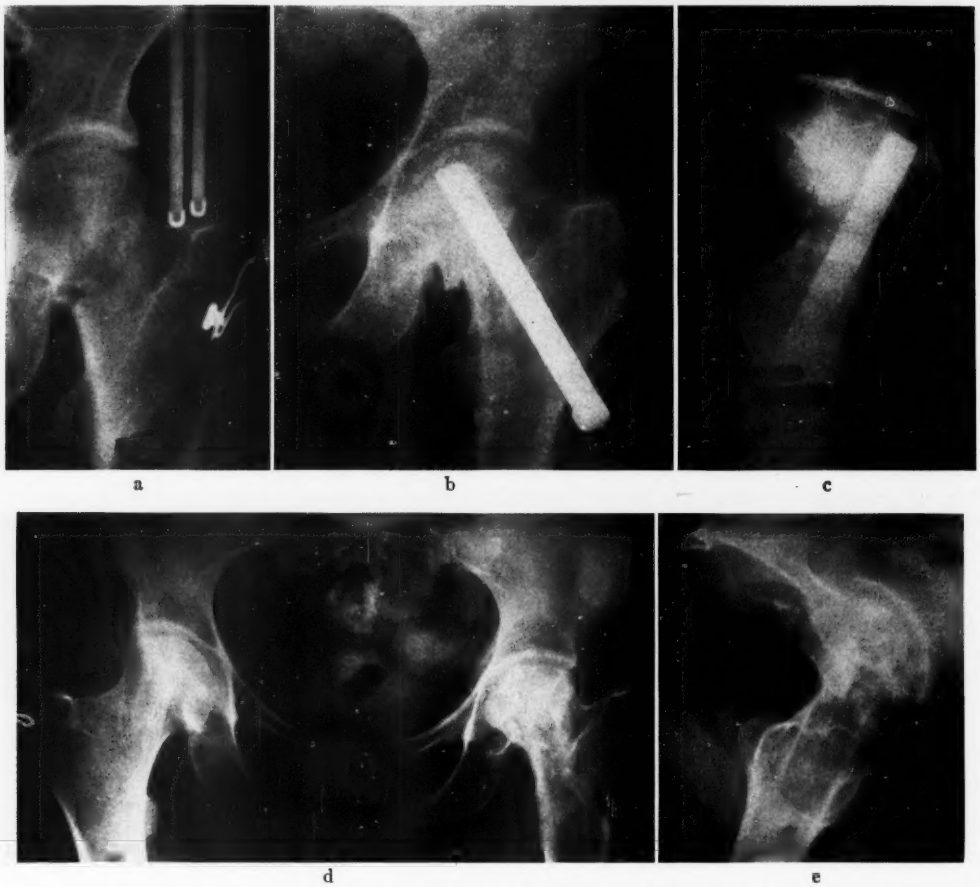


Fig. 1. Open reduction, nailing, extensive aseptic necrosis of femoral head. C. S., St. Luke's, No. A 05042. Female, 50 years old. Open reduction, fracture neck of left femur. a, b, and c, Fracture, reduction, and nailing, December 24, 1936. d and e, End result 3 years later after removal of nail. Some pain and limp.

turned to closed reduction of the fracture with internal fixation by the three-flanged nail. Careful roentgenographic supervision was utilized throughout the procedure. At the outset of this period, 1936, we began with various technical difficulties to utilize lateral roentgenograms of the femoral neck. In displaced fractures union was obtained in approximately 69 per cent of the cases, an obvious advance over our previous efforts.

During this period a series of 8 undisplaced fractures were treated by balanced suspension for 3 to 4 weeks and protected by a Thomas caliper hip splint, while ambulatory, for several months. Uncomplicated union of the fracture resulted in each instance.

3. *The second operative period 1941 to 1948.* We are adding an additional 125 cases, all subjected to closed reduction if displaced and all treated by three-flanged nail internal fixation. The end result is known in 118 of these 125 patients. Seventeen of these 118 failed to survive long enough to obtain union of the fracture, leaving 101 available for study as to union, nonunion, and circulatory disturbance in the femoral head.

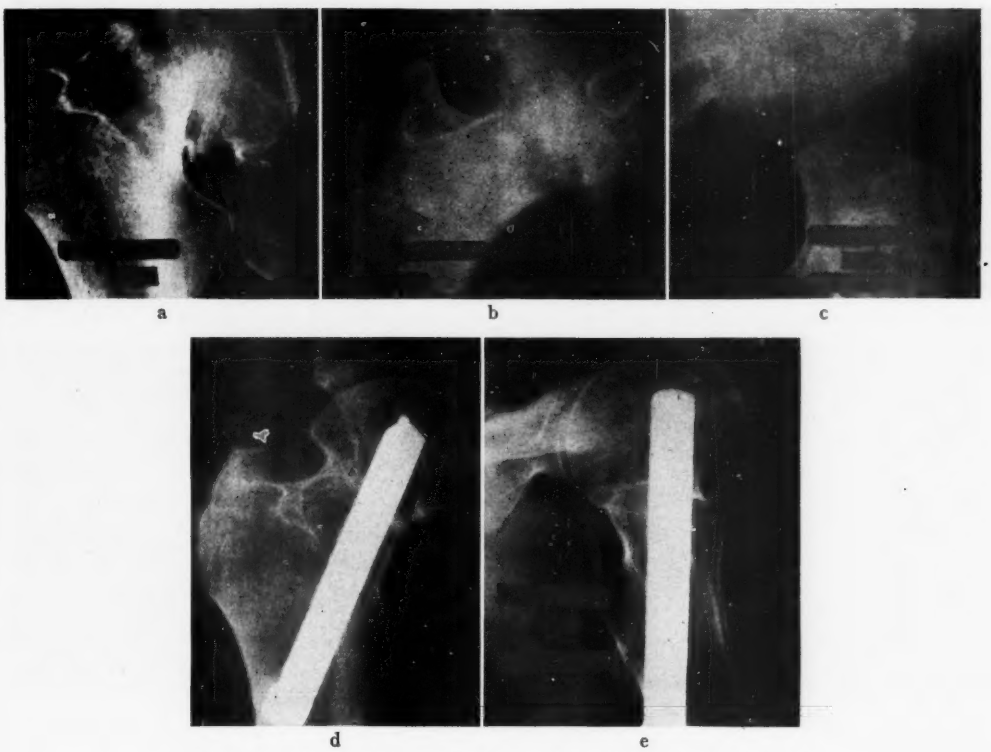


Fig. 2. Adequate reduction and internal fixation with uncomplicated union. L.D., St. Luke's, No. A 34240. Female, 73 years old. Closed reduction and internal fixation, fracture neck right femur. a, b, and c, Displaced fracture and adequate reduction. d and e, Uncomplicated union 3 years 11 months later and a satisfactorily placed nail. Excellent function.

If an adequate reduction of the displaced fracture is secured with firm, technically sound internal fixation, union of the fracture is more certain (Fig. 2). It has risen to almost 80 per cent of those surviving long enough to attain a united fracture.

REDUCTION OF THE FRACTURE

The reduction of this fracture is of the utmost importance and correct interpretation of the roentgenograms in two planes, which must be readily available, is of equal importance. Our failures to secure union and much of the ensuing circulatory disturbance in the femoral head are largely due to failure or inability to secure adequate reduction of the fracture and a proper insertion of the three-flanged nail in each instance. In other words, technical failure in the early treatment leaves the door wide open for poor end results which can be salvaged only with great difficulty in some instances, and often not at all (Fig. 3).

THE UNDISPLACED FRACTURE OF THE FEMORAL NECK

This fracture with minimal or no actual displacement affords an opportunity to compare our best efforts to secure reduction, to a fracture which needs no reduction. The undisplaced fracture seems to occur by the same mechanism as the displaced fracture and the difference has seemed to us to be one of degree of displacement. In this series of 235 femoral neck fractures there were 49 which showed

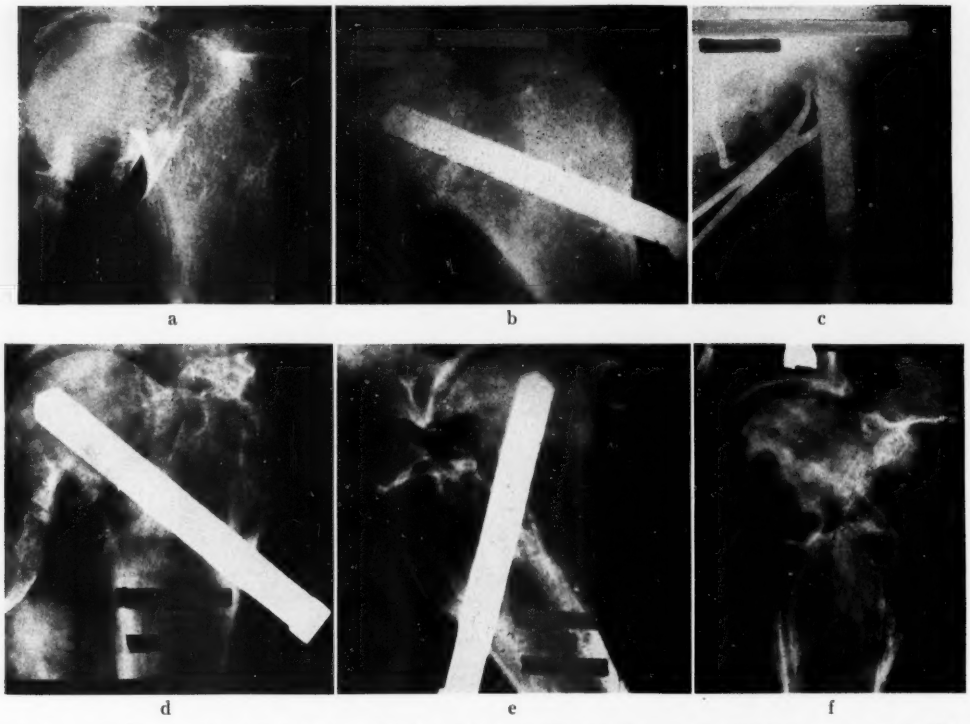


Fig. 3. Inadequate reduction and internal fixation with nonunion and salvage by osteotomy. J. B., St. Luke's, No. A 101-677. Female, 67 years old. Closed reduction and internal fixation, fracture, neck left femur. a, b, and c, Displaced fracture, poor reduction, and internal fixation. Nail barely within limits of femoral neck or head. d, e, and f, Later displacement of the fracture; a successful osteotomy. Walks with a limp, uses a cane.

little or no displacement of the fragments, an incidence of 20.8 per cent (Table I).

Prior to 1939, while we utilized internal fixation as our means of treating displaced fractures, we treated the undisplaced fractures with bed rest in balanced suspension, allowing ambulation at 3 to 4 weeks with a Thomas caliper hip splint with pelvic band. Union of the fracture with no circulatory disturbance occurred in each of the 8 treated by these conservative means (Fig. 4).

These undisplaced fractures require no reduction and 48 of the 49 have united, an incidence of 97.9 per cent. The single failure to unite occurred when the femoral head was displaced during nailing. This technical failure was unfortunately not recognized. Displacement of these undisplaced fractures may occur if unprotected weight bearing is allowed (Fig. 5). Because of this danger of displacement of this favorable type of fracture and in order to get the patients ambulatory at an earlier date, since 1939 we have fixed these fractures *in situ* with a three-flanged nail.

TABLE 1.—UNDISPLACED FRACTURES

	No.	Per cent
Total series	235	100
Undisplaced	49	20.8
Union	48	97.9
Nonunion	1	2.1

MORTALITY

Since the average age of these patients is very constantly in the middle sixties, death is bound to take its toll over the years. What really is significant is the mortality which may be directly attributed to the fracture with its attendant shock and the additional trauma

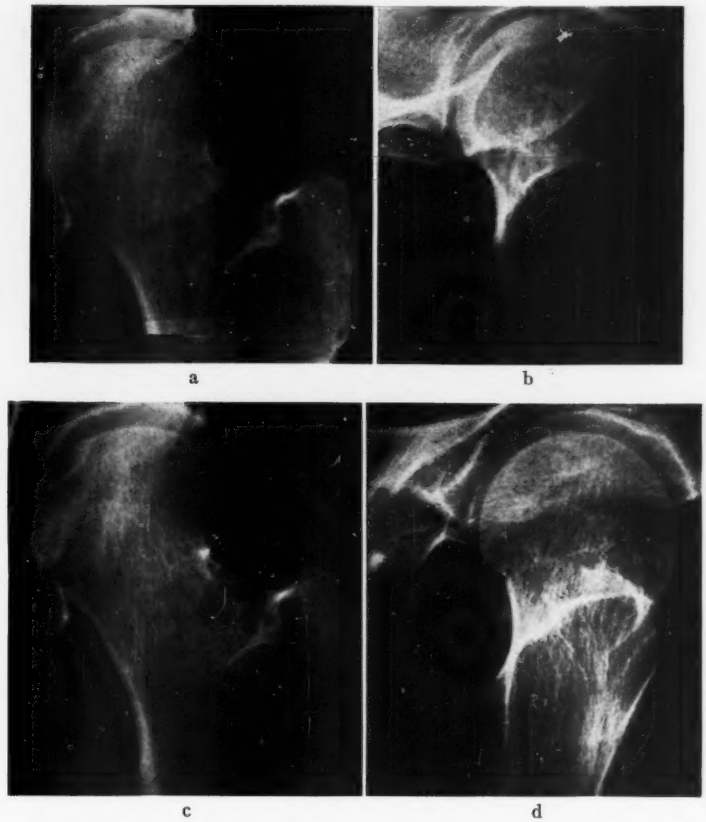


Fig. 4. Undisplaced fracture treated by conservative means. F. C., St. Luke's, No. A 26359. Female, 35 years old. Left femur. a and b, Original undisplaced fracture. c and d, Anteroposterior views 9 years later. Excellent function.

which a surgical procedure affords as shown in Table II.

Our first 50 patients, treated mainly by prolonged immobilization in plaster of paris, showed a 14 per cent mortality while in hospital. The second 60 patients treated during the transition period showed a mortality of 15 per cent while in hospital. This insignificant increase in mortality made us realize that these elderly patients could tolerate this type of surgery. Our final 125 patients have shown a mortality of only 7.2 per cent while in hospital. Since we have operated upon each intracapsular fracture of the femoral neck as it appeared almost without exception (the single exception recalled in the past 4 years was an elderly woman who reached the hospital moribund), this is indeed a creditable record. There has been no selection of cases in this series. This decrease in mortality while surgical treatment is utilized for every intracapsular fracture of the femur is an indication of improved operative technique. A constant effort

TABLE II.—MORTALITY

Period	No. of cases	Immediate mortality	
		No.	Per cent
1930–1935	50	7	14
1936–1941	60	9	15
1941–1948	125	9	7.2

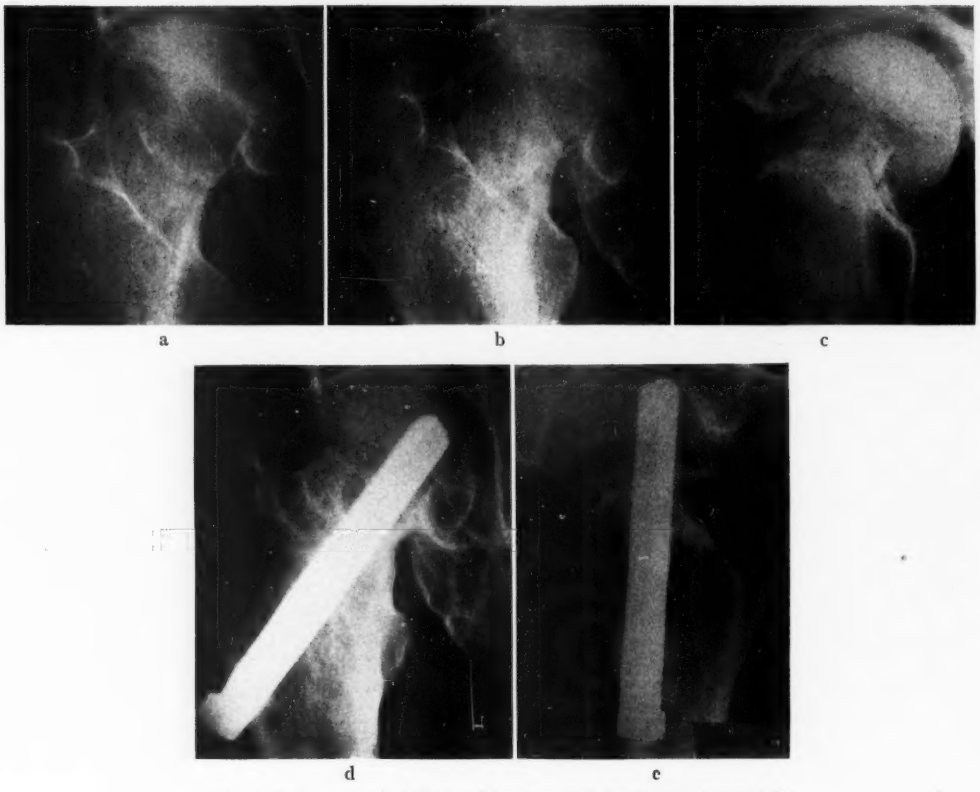


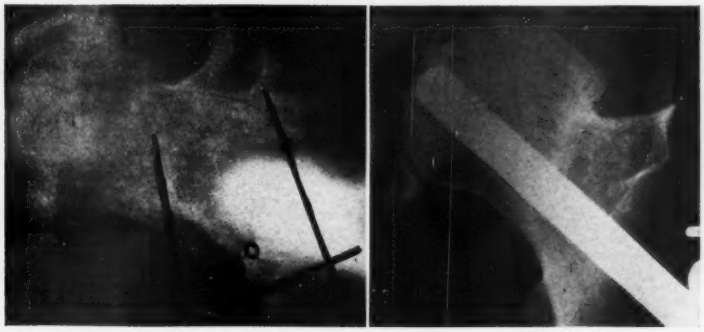
Fig. 5. Unrecognized undisplaced fracture with displacement on weight bearing. S. G., St. Luke's, No. A 144-636. Female, 85 years old. Closed reduction and internal fixation, fracture neck right femur. a, Unrecognized, undisplaced fracture. b and c, Displacement on weight bearing. d and e, One year and 3 months following operation with solid bony union. Excellent function.

is made to improve the nutrition and obviate the vitamin deficiencies of these elderly patients (4). In spite of their age and often debilitated state, surgical treatment of these fractures is relatively safe for these old people. There has been no actual operative death, i.e., within 1 week following operation, in our last 125 cases.

UNION OF THE FRACTURE

The undisplaced or minimally displaced fractures with the one exception noted previously have united (Table III).

This is, we believe, a fairly universal experience. Union in these undisplaced fractures is usually firm at 4 months after fracture. The real test of ability to secure union lies in the displaced fracture.' As has been noted previously, manipulative reduction (no lateral roentgenograms of the hip were then available) followed by such immobilization as a plaster of paris spica bandage affords, resulted in only 23.6 per cent united fractures (Table IV). Open reduction of the fracture with internal fixation, in a relatively small series, resulted in 50 per cent united fractures with a high incidence of circulatory disturbance in the femoral head. The first 33 cases of closed reduction and internal fixation, undisplaced fractures, resulted in 69.6 per cent union of



a b

Fig. 6. Intracapsular fracture, neck of femur; fracture line measuring 80 degrees to perpendicular of long axis of femur. Solid bony union. M. D., St. Luke's, No. A 96462. Female, 65 years old. Closed reduction and internal fixation, displaced fracture, left femoral neck. a, Fracture line at 80 degrees. b, Solid bony union, 3 years and 3 months later. Excellent function.

the fracture. The next 74 displaced fractures also treated by closed reduction and internal fixation have resulted in 79.7 per cent union of the fracture. Union of the displaced fracture, if it has been properly reduced and internally fixed, usually ensues at 7 to 9 months after fracture.

This is, of course, a record of steady improvement but we are still unable to secure union in approximately 1 out of every 5 of these displaced fractures. We are certain that our technical lapses are responsible for the persisting nonunion. In the last series of 125 femoral neck fractures presented, 14 of the 15 nonunions occurring in displaced fracture, among those patients surviving long enough to secure union were due to technical errors. These errors were: overdrive or otherwise faulty insertion of the nail, or inadequate reduction of the fracture or both. It has been stated that union is less apt to occur in a displaced fracture of the femoral neck, if the fracture surface forms an angle of 70 degrees or more to the perpendicular erected to the long axis of the shaft of the femur (5). In our last series there were 6 fractures in this category. With adequate reduction and internal fixation, union of the fracture resulted in 5. This is slightly better than our over-all record (Fig. 6).

TABLE III.—UNION IN UNDISPLACED FRACTURES

Period	Total No.	Union		Nonunion	
		No.	Per cent	No.	Per cent
No operation 1930–1935	10	10	100	0	0
No operation 1936–1939	8	8	100	0	0
Operation 1939–1948	31	30	96.7	1	3.3

CIRCULATORY DISTURBANCE IN THE FEMORAL HEAD

The extremely valuable and interesting report of the Fracture Committee of the American Academy of Orthopaedic Surgeons on "Treatment of Fracture of the Neck of the Femur by Internal Fixation" was a pioneer end result study on this subject. An attempt

TABLE IV.—UNION IN DISPLACED FRACTURES

Period	Total No.	Union		Nonunion	
		No.	Per cent	No.	Per cent
No operation 1930–1935	38	9	23.6	29	76.4
Open reduction 1936–1941	14	7	50	7	50
Closed reduction 1936–1941	33	23	69.6	10	30.4
Closed reduction 1941–1948	74	50	70.7	15	20.3

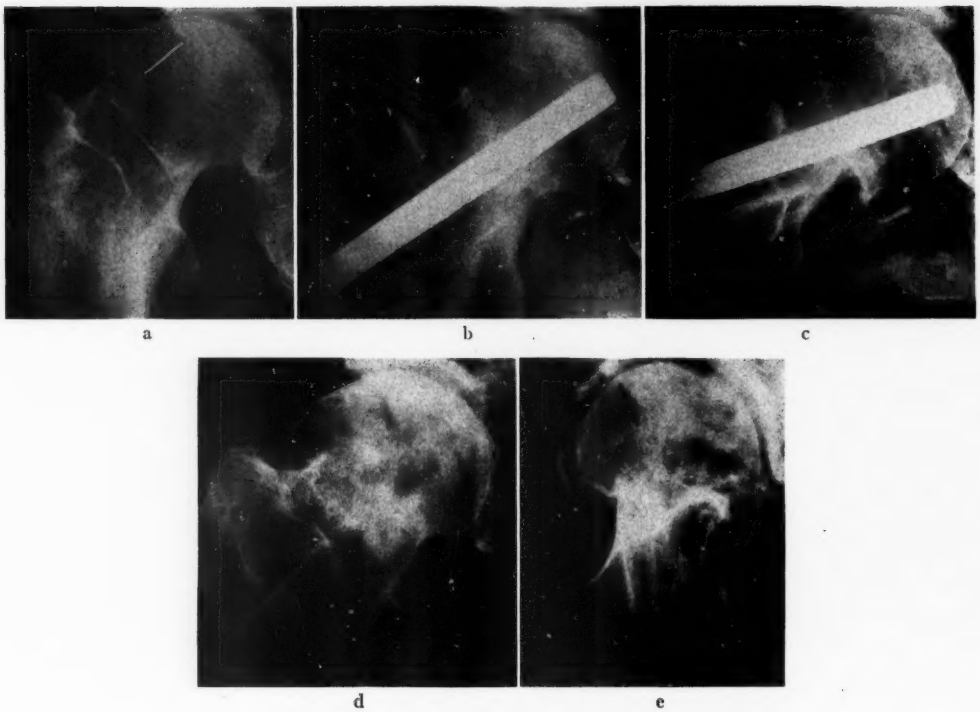


Fig. 7. Minimal circulatory disturbance of femoral head, asymptomatic. C. M., St. Luke's, No. A 48230. Male, 60 years old. Closed reduction and internal fixation, displaced fracture, right femoral neck. a, b, and c, Original fracture, slight deformity of head at 10 months after operation. d and e, Eight years after reduction and internal fixation. Symptom free, excellent function.

was made to grade circulatory disturbance in the femoral head, calling it "arthritic change." Only the most advanced grade was considered to be associated with aseptic necrosis of the femoral head. This series of 241 cases was collected from many surgeons and is bound to be influenced by wide variations in techniques and skills.

TABLE V.—CIRCULATORY DISTURBANCE OF THE FEMORAL HEAD IN DISPLACED FRACTURES

Period	United fractures	Aseptic necrosis	
		No.	Per cent
1930–1935	9	7	77.7
Open reduction 1936–1941	7	3	42.8
Closed reduction 1936–1941	23	7	30.4
Closed reduction 1941–1948	59	9	15.2

In attempting to compare our experience in circulatory changes in the femoral head with that of the Fracture Committee of the American Academy, we run into some difficulty. We have considered any change in the femoral head after union of the fracture as due to some circulatory disturbance.

Our total incidence of aseptic necrosis of the femoral head in 89 displaced fractures treated by reduction and internal fixation has been 21.3 per cent compared to 26.6 per cent reported by the Fracture Committee in a series of 105 united fractures originally displaced, reduced and fixed by a three-flanged nail, and 33 per cent reported by Boyd and George in their report on 132 displaced fractures of the

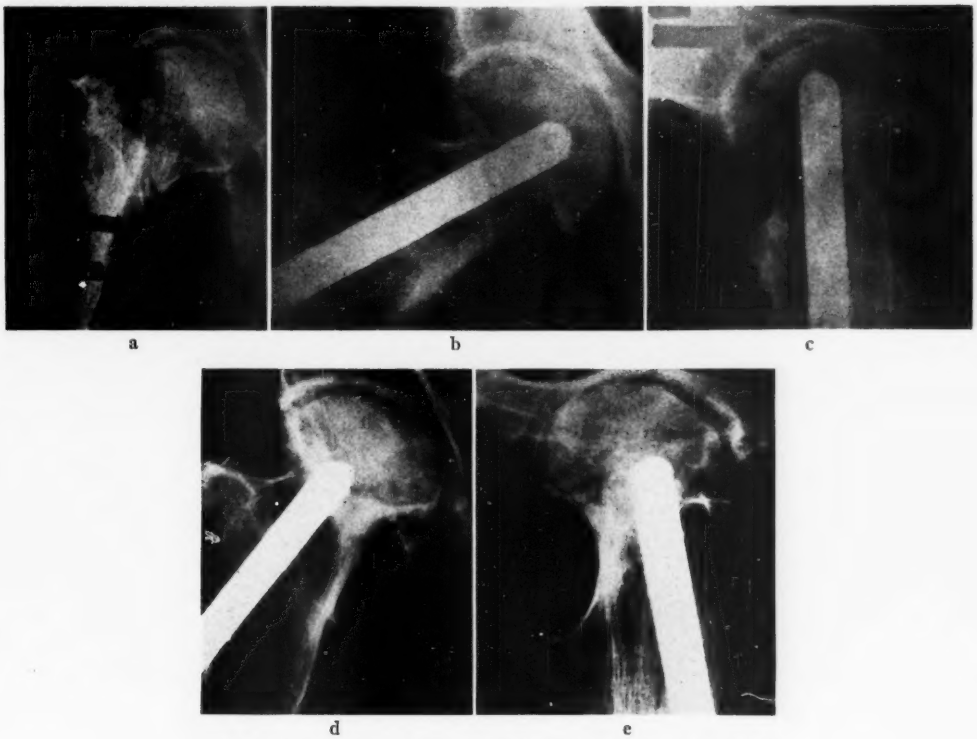


Fig. 8. Aseptic necrosis, femoral head following adequate reduction and internal fixation. K. C., St. Luke's, No. A 117-103. Female, 80 years old. Closed reduction and internal fixation, displaced fracture, femoral neck. a, Original fracture. b and c, Adequate reduction and internal fixation. d and e, Aseptic necrosis 1 year and 11 months after operation. This patient had a painful, stiff hip. (Roentgenographic evidence of circulatory disturbance was noted 1 year after fracture.)

femoral neck, similarly treated, which united. This circulatory disturbance in the femoral head in the united femoral neck fracture remains an important obstacle to the achievement of an excellent result. The symptoms vary from a slight limp with pain to marked progressive disability associated perhaps with complete loss of motion at the hip joint. At times these circulatory changes are noted by roentgenogram in patients who have no symptoms and little or no evidence of disability.

In our first series of 50 cases there were 9 displaced fractures which united and 77.7 per cent of these showed aseptic necrosis of the femoral head (Table V). The open reduction with internal fixation of the fracture showed an incidence of 42.8 per cent of aseptic necrosis in those fractures which united. The reduction of these fractures was often unsatisfactory and the technique of open nailing left much to be desired.

TABLE VI.—CIRCULATORY DISTURBANCE OF THE FEMORAL HEAD IN UNDISPLACED FRACTURES

Period	United fractures	Aseptic necrosis	
		No.	Per cent
1930–1935	10	2	20
No operation 1936–1941	8	0	0
Operation 1939–1948	31	4	13

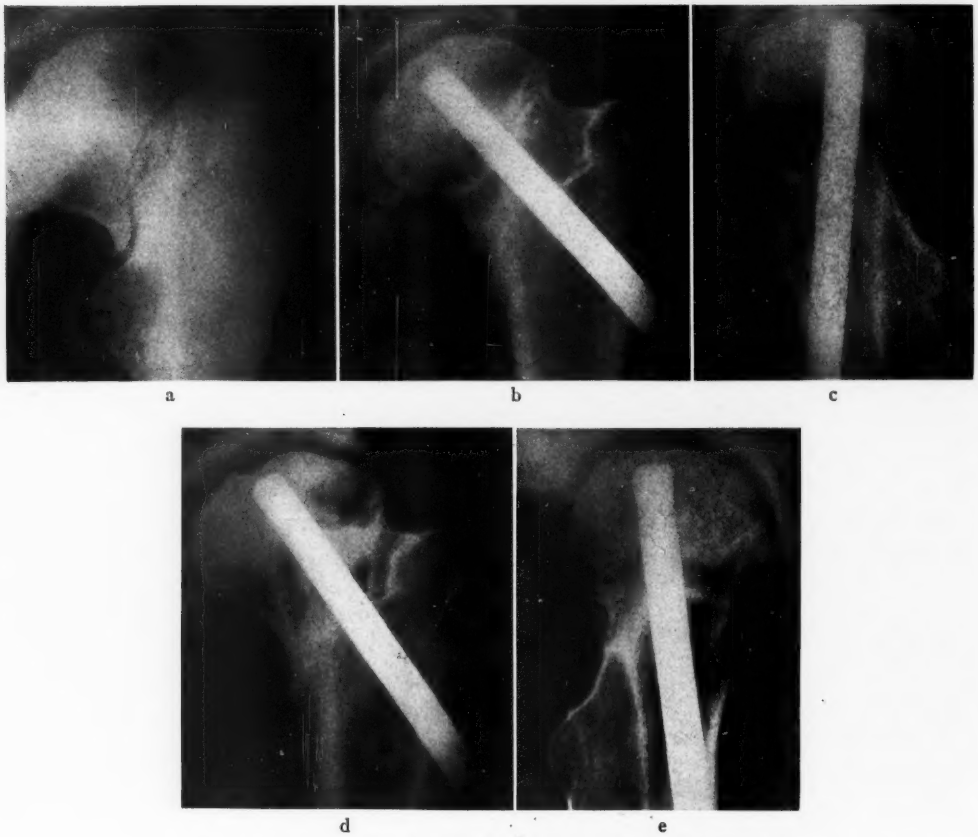


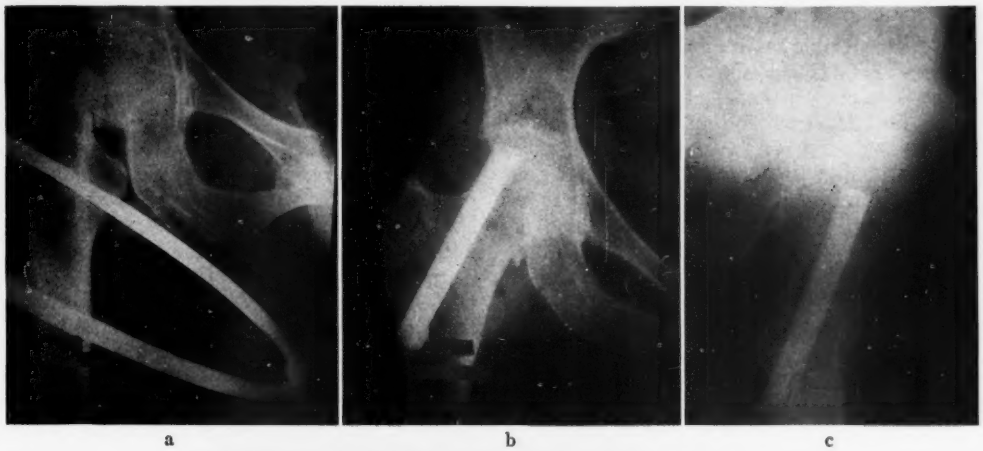
Fig. 9. Aseptic necrosis of femoral head discovered 4 years after reduction and internal fixation. T. K., St. Luke's, No. A 17967. Male, 51 years old. Closed reduction and internal fixation, displaced fracture, left femoral neck. a, Original fracture, 6–12–39. b and c, Anteroposterior and lateral views 2 years later, showing minimal deformity of femoral head. d and e, Marked aseptic necrosis of the femoral head 4 years after reduction and internal fixation. At this time patient returned to the outpatient department because of stiffness in the hip.

The first 23 displaced fractures, treated by closed reduction and internal fixation which united have shown on late follow-up, 30.4 per cent incidence of aseptic necrosis of the femoral head. About half of these have been merely a roentgenographic finding without any evidence of pain, limp, or limited motion in the hip joint (Fig. 7).

Our last 59 displaced fractures of the femoral neck which united after reduction and fixation by the three-flanged nail, showed an incidence of 15.2 per cent aseptic necrosis of the femoral head.

CIRCULATORY DISTURBANCE IN THE UNDISPLACED FRACTURE OF THE FEMORAL NECK

The incidence of aseptic necrosis in the undisplaced fractures of the femoral neck is indicated in Table VI. The incidence was 20 per cent in the first series and these are believed to have been the result of vigorous and unnecessary manipulation in an at-



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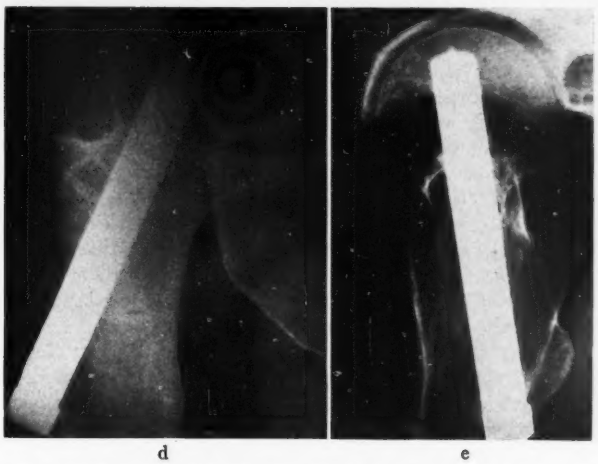

d e

Fig. 10. Uncomplicated union, displaced intracapsular fracture 10 year result. M. D., St. Luke's, No. A 3458. Female, 63 years old. Closed reduction and internal fixation, displaced fracture, right femoral neck. a, Original fracture. b and c, Immediate postoperative reduction and nailing. d and e, Uncomplicated union 10 years after reduction. Excellent function. This hip was not perfectly reduced, nor was the nailing optimum.

tempt to reduce a fracture which required no reduction.

The second series of undisplaced fractures of the femoral neck treated by balanced suspension and later protected by a Thomas caliper hip splint showed healing of the fracture with no evidence of aseptic necrosis. This record in a small series makes us pause to consider whether simple protection of the undisplaced fracture of the femoral neck should be practiced rather than internal fixation.

Of the 31 undisplaced fractures which were treated by internal fixation, aseptic necrosis resulted in 4 instances, or 13 per cent.

The incidence of aseptic necrosis in the femoral head in the displaced fracture is approaching that which occurs in the undis-

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placed fracture. Whether or not we are reaching an irreducible minimum again remains to be determined. In some instances aseptic necrosis is due to technical failure to secure optimum reduction and internal fixation of maximum efficiency. Five of the 12 instances of aseptic necrosis of the femoral head in united fractures, in our latest series, were associated with technical failures, such as overdrive of the nail in 1 instance and inadequate reduction of the fracture or other technical faults in insertion of the nail in the other 4 instances.

With equal frequency we are quite unable to explain the appearance of this complication (Fig. 8).

In a previous report we (3) made the statement that "circulatory disturbance in the femoral head based on our experience with these 60 patients has always appeared within the first year after fracture." This was perhaps too dogmatic and later experience leads us to modify this statement, however only slightly. Our patients come from no great distance and repeated examinations and roentgenograms have been made during the 30 months' period after the fracture. In only 1 instance have we seen aseptic necrosis of the femoral head occur after the first 18 months following a united fracture of the neck of the femur and in this instance the first roentgenogram after leaving the hospital at 26 months shows minimal change in the femoral head; and at 4 years after fracture the changes were pronounced and symptoms of pain and stiffness ensued (Fig. 9).

This observation holds for 89 displaced fractures which have united and have been followed for an average of nearly 3 years. Forty-eight of these fractures have been followed and checked by roentgenograms for 3 to 10 years after the fracture (Fig. 10).

DEGENERATIVE ARTHRITIS OF THE HIP JOINT

This complication has not been encountered in our experience in otherwise uncomplicated intracapsular fractures of the femoral neck. In each instance it has been part of the picture of circulatory disturbance or aseptic necrosis. This degenerative arthritis is, we believe, a sequel or concomitant factor of impaired circulation of the femoral head rather than a separate entity.

RESULTS

In order to evaluate the end result of a fracture of the neck of the femur, one should be certain what the patient could do before he or she sustained the fracture. If patients were not able to walk prior to fracture, it is a bit simple minded to expect the operation to put them on their feet. We believe that a united fracture without circulatory disturbance in the femoral head which is sufficient to produce pain, limp, or disability, constitutes a good or satisfactory end result. On this basis we find that we have been able to secure union without complications in 67.5 per cent of the last 74 displaced fractures.

SUMMARY

A series of 125 consecutive patients with intracapsular fractures of the neck of the femur is presented and compared with two previously reported series of 50 and 60 each, also consecutive.

This latest series of patients were all treated by closed reduction of the fracture if it was displaced, and all of them had internal fixation with a three-flanged nail.

We know the end result in 118 of these 125 patients—a 94.4 per cent follow-up. Mortality has dropped from 14 and 15 per cent respectively in the first two series to 7.2 per cent in this latest 125 patients. There were no operative deaths.

Union ensued in all but 1 of the 31 undisplaced fractures, in approximately 4 months. Union in the latest 74 displaced fractures has ensued in 79.7 per cent, a definite improvement over our previous record. These displaced fractures have united 7 to 9 months after reduction and fixation.

Circulatory disturbance or aseptic necrosis has dropped to 15.2 per cent in the last 59 displaced fractures which have united—a very marked improvement over our previous record. With 1 possible exception, we have not seen these circulatory changes take place in the femoral head after the first 18 months following reduction. If a patient has a good

result at 18 months, the condition should continue to persist.

Circulatory disturbance of the femoral head occurred in 4 of the 31 undisplaced fractures subjected to internal fixation—or 13 per cent. While 8 successive undisplaced fractures treated previously by suspension and later protected with a brace showed no incidence of circulatory disturbance, we still feel that careful internal fixation is preferable.

Degenerative arthritis has been found only as part of the picture of circulatory disturbance of the femoral head.

The average follow-up has been 30 months for all patients and we have 48 patients followed from 3 to 10 years after treatment.

Putting forth our best efforts in technique we are as yet able to get uncomplicated union of the displaced fractures, a completely satisfactory result, in only 2 out of every 3 cases.

Our experience leads us to believe that the best means to secure this optimum result is anatomic reduction and firm, technically sound internal fixation.

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REGIONAL HEPARINIZATION IN VASCULAR SURGERY

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IN his classic monograph on "Thrombosis," Welch (9) in 1909 wrote, "The recognition of the three classes of causes assigned for thrombosis, namely, alterations in the blood, mechanical disturbances of the circulation, and lesions of the vascular or cardiac wall, is not of recent date." In his studies on the structure of white thrombi published in 1887 (8) he observed, "it is possible to produce experimentally severe injury of the internal coats of blood vessels without any resulting thrombosis. Slowing of the circulation and irregularities of the circulation produced by abnormalities in the lumen of the blood vessels are factors no less important in the production of thrombi than alterations in the vessel walls." During surgery of large arteries there is necessarily some injury to the intima. Spasm of the affected vessel may lead to a slowing of the circulation and even a slight irregularity of the lumen may produce sufficient distortion to bring about irregularities of the circulation. Under such circumstances thrombosis is likely to occur unless the blood which traverses the suture line is kept from clotting by the administration of an anticoagulant.

Heparin was discovered by McLean, working in Howell's laboratory, in 1916. Extensive use of this substance, however, was not possible until methods for its extraction and purification were developed by Charles and Scott under the direction of Best in 1935. It was soon demonstrated by Murray and his coworkers (6) that the parenteral administration of heparin in experimental animals could prevent the development of thrombosis following injury of the major blood vessels. In 1937 they reported the results in a series of dogs in which the external jugular vein had been subjected to mechanical or chemical trauma. Thrombosis with occlusion took place in a high percentage of the control animals. When, under similar conditions, heparin was given occlusion did not take place. Murray, in 1940 (3), reported that, "From several hundred experiments it appeared that heparin was effective when adequate concentrations were maintained in the blood stream."

Heparin was also found to be helpful in the prevention of thrombosis following the surgery of arteries in the experimental animal. Murray (3) reported that in over 50 experiments in which heparin was used, the arteries remained patent in more than 80 per cent, as compared with 35 per cent for the controls. Similarly it was possible to bridge the gap in arteries by the insertion of vein grafts. When thrombosis was prevented by the administration of heparin, the continuity of the vessel was restored. Finally, in the treatment of experimental arterial embolism, he showed that the obstruction could be successfully removed even up to 3 days after insertion of a foreign body and in spite of the inflammatory reaction present in the vessel walls.

In 1941, Murray (4) reported 7 cases in which arterial surgery had been successfully performed with the help of heparinization. The heparin was given by continuous intravenous drip for a period of from 3 to 8 days. The clotting time was maintained at approximately 15 minutes. Since this time numerous other workers have reported the successful use of heparinization after the surgery of major arteries. Shumacker and his associates reported 22 cases in which various types of arterial repair had been carried out with the use of anticoagulants. Heparin was given intravenously at the time of operation and was continued only during the initial period of dicumarol therapy until a satisfactory alteration of prothrombin activity had been obtained. They reported occasional instances of bleeding from

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small vessels in the wound when the clotting time of the general blood stream had been raised by heparinization.

In addition to general heparinization Murray and Best (5) described regional heparinization. This term was coined to describe the injection of heparin into an artery in such an amount as to affect the clotting time locally and in the vein draining the limb without change of the clotting time in the general blood stream. In arterial anastomosis the heparin solution was injected through a needle inserted into the artery just above the suture line. The advantage of regional heparinization lies in the fact that the blood coming into contact with the injured segment of vessel is rendered incoagulable, and, at the same time, the danger of bleeding in the wound is minimized.

The present communication deals with the use of regional heparinization in patients following the removal of arterial emboli and following repair of arteries after trauma and after excision of an aneurysm.

Fig. 1, at left. Left femoral arteriogram, Case 1, showing obstruction of common femoral, profunda and superficial femoral arteries.

Fig. 2. Arteriogram, Case 1, 7 weeks after removal of embolus from left common femoral artery and thrombus from superficial femoral artery. Irregularities of the lumen at the sites of 4 arteriotomy openings are visualized.

CASE REPORTS

CASE 1. C. H. G., University of California Hospital No. 154628. The patient was a white male, aged 39 years, admitted to the University of California Hospital on June 6, 1948, with a chief complaint of pain and numbness of the left leg of 24 hours' duration. He had been aware of the fact that he had heart disease for a period of 6 years when the diagnosis of mitral stenosis had been made. There was no history of rheumatic fever, but he had been told that he had suffered from rheumatic heart disease. There were progressive symptoms of pulmonary congestion with cough, exertional dyspnea, and orthopnea. Twenty-four hours before admission the patient had noted a sudden onset of a tingling sensation with pain and numbness of the left foot. The symptoms rapidly progressed up to the mid-thigh and the foot became cold. He was given an injection of morphine with some relief of his symptoms.

On admission, physical examination revealed his heart was enlarged to the left with a short presystolic apical murmur, noted with the patient lying on his left side. There were frequent extrasystoles. The femoral pulse was excellent on the right, but on the left it was palpable for but a short distance below the inguinal ligament. Ankle pulses were not palpable on either side. The left leg showed cyanosis and coldness extending up to the mid-thigh and anesthesia with paralysis of the foot. There was no induration of the calf muscles. Arteriography of the left femoral (Fig. 1) showed a complete obstruction of the common femoral artery as well as an occlusion of the superficial femoral down to 1½ inches above the knee joint. Under continuous spinal anesthesia, a long incision was made over the femoral vessels from the inguinal ligament to the level of the adductor tubercle. The common femoral was occluded by a firm organized thrombus without pulsation in the profunda or superficial femoral arteries. The profunda and the superficial femoral were occluded by segments of rubber tubing and a similar tube was placed about the common femoral. A short transverse incision was made in the common femoral just above the origin of the profunda. With pressure on the superficial femoral and upon the profunda the thrombus was removed from the bifurcation, and retrograde bleeding from the profunda was apparent although not from the superficial femoral. Upon release of the tourniquet above the site of the embolus, it could be demonstrated that the common femoral artery was free of both the embolus and thrombus. A 22 gauge needle, 4 inches in length, was then inserted into the common femoral artery above the tourniquet and heparin solution—100 milligrams in 500 cubic centimeters of 5 per cent glucose in distilled water—was slowly injected. The opening in the common femoral artery was then closed with a continuous suture of No. 00000 Deknatel. Upon release of the tourniquet the blood flowed freely past the suture line and down the profunda so that good pulsations were palpable. However, the superficial femoral artery was still occluded by the thrombus.

REGIONAL HEPARINIZATION IN VASCULAR SURGERY

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IN his classic monograph on "Thrombosis," Welch (9) in 1909 wrote, "The recognition of the three classes of causes assigned for thrombosis, namely, alterations in the blood, mechanical disturbances of the circulation, and lesions of the vascular or cardiac wall, is not of recent date." In his studies on the structure of white thrombi published in 1887 (8) he observed, "it is possible to produce experimentally severe injury of the internal coats of blood vessels without any resulting thrombosis. Slowing of the circulation and irregularities of the circulation produced by abnormalities in the lumen of the blood vessels are factors no less important in the production of thrombi than alterations in the vessel walls." During surgery of large arteries there is necessarily some injury to the intima. Spasm of the affected vessel may lead to a slowing of the circulation and even a slight irregularity of the lumen may produce sufficient distortion to bring about irregularities of the circulation. Under such circumstances thrombosis is likely to occur unless the blood which traverses the suture line is kept from clotting by the administration of an anticoagulant.

Heparin was discovered by McLean, working in Howell's laboratory, in 1916. Extensive use of this substance, however, was not possible until methods for its extraction and purification were developed by Charles and Scott under the direction of Best in 1935. It was soon demonstrated by Murray and his coworkers (6) that the parenteral administration of heparin in experimental animals could prevent the development of thrombosis following injury of the major blood vessels. In 1937 they reported the results in a series of dogs in which the external jugular vein had been subjected to mechanical or chemical trauma. Thrombosis with occlusion took place in a high percentage of the control animals. When, under similar conditions, heparin was given occlusion did not take place. Murray, in 1940 (3), reported that, "From several hundred experiments it appeared that heparin was effective when adequate concentrations were maintained in the blood stream."

Heparin was also found to be helpful in the prevention of thrombosis following the surgery of arteries in the experimental animal. Murray (3) reported that in over 50 experiments in which heparin was used, the arteries remained patent in more than 80 per cent, as compared with 35 per cent for the controls. Similarly it was possible to bridge the gap in arteries by the insertion of vein grafts. When thrombosis was prevented by the administration of heparin, the continuity of the vessel was restored. Finally, in the treatment of experimental arterial embolism, he showed that the obstruction could be successfully removed even up to 3 days after insertion of a foreign body and in spite of the inflammatory reaction present in the vessel walls.

In 1941, Murray (4) reported 7 cases in which arterial surgery had been successfully performed with the help of heparinization. The heparin was given by continuous intravenous drip for a period of from 3 to 8 days. The clotting time was maintained at approximately 15 minutes. Since this time numerous other workers have reported the successful use of heparinization after the surgery of major arteries. Shumacker and his associates reported 22 cases in which various types of arterial repair had been carried out with the use of anticoagulants. Heparin was given intravenously at the time of operation and was continued only during the initial period of dicumarol therapy until a satisfactory alteration of prothrombin activity had been obtained. They reported occasional instances of bleeding from

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small vessels in the wound when the clotting time of the general blood stream had been raised by heparinization.

In addition to general heparinization Murray and Best (5) described regional heparinization. This term was coined to describe the injection of heparin into an artery in such an amount as to affect the clotting time locally and in the vein draining the limb without change of the clotting time in the general blood stream. In arterial anastomosis the heparin solution was injected through a needle inserted into the artery just above the suture line. The advantage of regional heparinization lies in the fact that the blood coming into contact with the injured segment of vessel is rendered incoagulable, and, at the same time, the danger of bleeding in the wound is minimized.

The present communication deals with the use of regional heparinization in patients following the removal of arterial emboli and following repair of arteries after trauma and after excision of an aneurysm.

Fig. 1, at left. Left femoral arteriogram, Case 1, showing obstruction of common femoral, profunda and superficial femoral arteries.

Fig. 2. Arteriogram, Case 1, 7 weeks after removal of embolus from left common femoral artery and thrombus from superficial femoral artery. Irregularities of the lumen at the sites of 4 arteriotomy openings are visualized.

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Fig. 3. Arteriogram, Case 2, of left brachial artery 5 weeks after resection of 1½ inches of vessel with end-to-end anastomosis.

It was accordingly opened at three additional levels—in the upper, the mid, and lower thirds of the thigh. Through these incisions the thrombus was extracted and each arteriotomy opening closed in turn. At the conclusion of this procedure excellent pulsation was palpable in the artery below the lowest incision. The needle was left in the common femoral artery and brought out through the upper end of the wound, and the injection of heparin solution was maintained for 9 hours by means of a continuous drip. It then became apparent that the adapter had become detached from the needle. The needle was then withdrawn. Immediately after operation, the circulation had partly returned to the left foot, although it was still cold and pulseless. However, in subsequent days the hypesthesia became less marked and the motor power in the left foot returned to normal. Arteriogram was repeated on July 23 with the injection of 8 cubic centimeters of thorotrast into the left femoral artery just distal to the inguinal ligament. Serial films (Fig. 2) showed that the continuity of the left femoral artery had been completely re-established.

In spite of the fact that this patient was not operated upon until 29 hours after the lodgment of the embolus in his left common femoral artery, and in spite of the fact that there was extensive thrombosis both proximally and distally involving the common femoral and the superficial femoral arteries, the embolus and the thrombi were successfully removed through four arteriotomy incisions. Regional heparinization prevented the formation of thrombi at the arteriotomy openings.

Case 2. L. S., St. Mary's Hospital No. 152185. The patient was a 35 year old white male, who on December 15, 1948, had his left arm just above the elbow caught between two steel beams. There was a small puncture wound on the medial side of the arm 3 inches above the elbow, but no fracture. Immediately tense swelling occurred with anesthesia and paralysis of the hand and forearm. When he was examined 4 hours after injury, wristdrop was present with complete anesthesia of the hand to the midforearm. The hand was cold, no pulses were palpable at the wrist, and the veins were distended over the forearm. The muscles of the forearm below the elbow were markedly tense, and the swelling extended to the upper third of the arm. It was not pulsatile, but on auscultation Korotkoff sounds could be heard over the course of the brachial artery above the swelling. With a diagnosis of laceration of the brachial artery the patient was taken to the operating room and with a tourniquet applied just below the axilla, the hematoma was widely opened. The brachial artery was found to have been completely ruptured, except for a small strand of adventitia over a distance of 1½ inches. Rubber tubes were placed about the brachial above and below the point of rupture and the tourniquet removed. Excellent pulsation was present at the proximal end, but there was no back bleeding from the distal end. When the blood was forced back into this end, wide extravasation over a distance of 1 inch was present, indicating extensive injury to the vascular wall. The proximal end of the brachial artery was dissected free, the adventitia excised, and the traumatized end of the vessel resected. The lower segment was dissected down to the antecubital space and a segment 1½ inches in length was excised. No important collaterals were sacrificed. The lower segment was then surrounded by segment of umbilical tape, the upper with a segment of rubber tubing, and the two ends approximated. With the elbow in acute flexion it was possible to bring the ends of the brachial artery together so that a circular anastomosis was possible. using a continuous everting mattress suture of No. 00000 Deknatel. Before release of the constricting rubber tube about the upper end of the vessel, a 27 gauge needle connected by means of a segment of rubber tubing to a 50 cubic centimeter syringe was inserted into the brachial artery above the point of occlusion and heparin solution—100 milligrams in 500 cubic centimeters of saline solution—was slowly injected over a period of 20 minutes. At this time excellent pulsation was present in the brachial artery below the suture line. Since some bleeding was taking place from this suture line, the hypodermic needle was removed. At the conclusion of the operation the radial pulse was readily palpable. The arm was placed in acute flexion at the elbow by means of a posterior plaster splint for a period of 10 days and then gradually the patient was allowed to extend his arm. Arteriogram 5 weeks after injury (Fig. 3) showed a normal restoration of continuity of left brachial artery. The nerve lesions cleared up rapidly.

Regional heparinization was carried on for a period of 20 minutes following end-to-end anastomosis of a ruptured brachial artery in which it had been necessary to excise 1½ inches of traumatized vessel. At the end of this time there was evidence of pulsatile flow of blood across the suture line without spasm of the proximal or distal segments of the artery.

CASE 3. W. Z. H., Franklin Hospital No. 20781. The patient was a 66 year old white man, admitted on January 30, 1949, with a diagnosis of embolism of the left femoral artery. This patient had been in poor health for the previous 2 years and had been receiving digitalis because of symptoms of congestive heart failure. One week before admission he had suffered what was termed a mild "stroke" with a partial motor aphasia. Upon again becoming ambulatory he had noted pain in both calves on walking two blocks. At 11 o'clock in the morning of his admission he developed a sense of tiredness in his left leg, followed shortly by numbness and tingling of the left foot and cramp-like pain in the calf. He was seen by a physician who performed a lumbar sympathetic block with procaine and administered heparin, but without relief. Accordingly, he was admitted to the hospital. Upon admission, his blood pressure was 210–110, and his pulse was totally irregular. The left lower extremity was cyanotic up to the knee, with cutaneous anesthesia extending to 10 centimeters below the knee joint, and motor paralysis of the foot and ankle. Pulsation of the femoral artery could be felt just below the inguinal ligament, but not below this point. The pulses in the right lower extremity were normally present. Oscillometry revealed no pulsation of the arteries below the knee on the left side and a barely detectable oscillation above the knee.

The patient was operated upon 8 hours after the initial symptoms. Under local anesthesia a curved incision was made below Poupart's ligament extending down along the femoral canal to expose the vessels. The common femoral artery was obstructed by a firm thrombus, but pulsation could be felt at the upper end of the exposure. The superficial femoral artery and profunda femoris were surrounded by segments of rubber tubing and a third segment of rubber tubing was placed about the common femoral above the thrombus. A transverse incision was made in the superficial femoral just distal to the profunda and a firm gray thrombus which was not adherent to the vessel wall was extruded by gentle pressure. Some retrograde bleeding, but at a low pressure, was observed. The profunda femoris was treated in a similar fashion. These arteries were again both occluded while the rubber tubing around the common femoral was loosened, and by gentle pressure the clot was delivered from the arteriotomy opening. After again occluding the common femoral artery the lumen of the vessel was irrigated with heparin solution—100 milligrams in 500 cubic centimeters of 5 per cent glucose in distilled water. A yellow calcareous plaque was present on the posterior wall of the femoral artery. The arteriotomy opening was closed with a continuous running stitch of No. 00000 Deknatel. A 22 gauge needle, 4 inches long, connected by way of a segment of rubber tubing to a 50 cubic centimeter syringe, was then inserted through the skin above the operative wound and brought into the operative field (Fig. 4). The needle was then inserted into the common femoral artery above the highest segment of rubber tubing. This heparin solution was injected into the arteries as the sections of tubing about the superficial femoral, profunda, and common femoral arteries were successively released. Approximately 75 cubic centimeters of heparin solution were injected, and when the superficial femoral artery became dilated below the suture line, the needle was withdrawn and the wound closed in layers. After operation, even though oscillometry showed reduced pulsation below the knee, the oscillations above the knee were very large. At the conclusion of the operation, sensation and motion had returned to the foot and toes, although they were still cool.

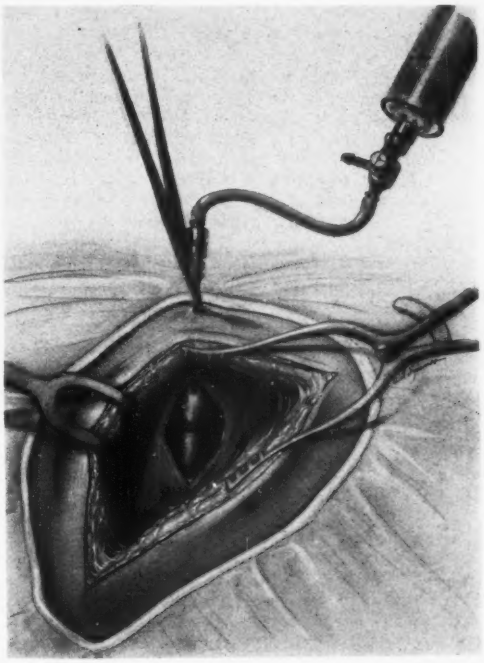

Fig. 4. Regional heparinization carried out in Case 3 by injection of heparin solution by means of a needle inserted through the skin and into the femoral artery above the line of suture.

Immediately after operation the patient was given heparin, 50 milligrams, intravenously every 4 hours and 300 milligrams of dicumarol. However, he developed a large hematoma in his wound with necrosis of the wound margins. On the 18th postoperative day, while the patient was still under dicumarol therapy, a débridement of the wound was performed. After hemostasis had been obtained, the deep fascia was approximated with interrupted sutures and the skin left open. However, he continued to bleed so that it was again necessary to open the wound to secure the bleeding points. The edges were brought together with adhesive tape, and healing took place without further difficulty.

This patient was placed on prolonged anticoagulant therapy with dicumarol in order to prevent further embolism associated with his auricular fibrillation. Recurrent hemorrhage from the operative wound was a serious complication in his case. Six months after operation the patient reported that no further trouble had been encountered.

CASE 4. A. B., Franklin Hospital No. 20340. This 61 year old white female, was admitted to the hospital on February 9, 1949. Four days prior to admission the patient developed a sudden, severe pain in the right hip with numbness of the right leg and coldness of both legs. The pain on the right side disappeared in 24 hours. Three days prior to entry she suddenly developed pain in the left hip and groin which persisted so that heavy narcotics were required. The patient had had rheumatic fever at the age of 11 and had developed a heart murmur subsequently. Auricular fibrillation had been present for several years.

On examination the heart was enlarged and the radial pulse totally irregular. No pulsation was present in either femoral artery. On the left side it was possible to feel a mass approximately 2 by 1 centimeter in the left groin. The right leg was cool but the color was normal, and sensation, though diminished, was present to the toes. On the left side total anesthesia was present from the mid-thigh to the toes, with complete paralysis and a wooden hardness of the muscles of the leg. Oscillometric examination disclosed barely perceptible oscillations in the left upper thigh and none on the right side. The patient was given 6 cubic centimeters of cedilanid intravenously and the heart rate dropped from 130 to 96. When her general condition had improved she was taken to the operating room and under endotracheal anesthesia through a transverse incision below the umbilicus on the left side, the left iliac artery and terminal aorta were exposed retroperitoneally. The bifurcation of the aorta was found to be occluded by a firm thrombus. The aorta and both iliac arteries were surrounded by segments of rubber tubing and the terminal aorta was opened transversely to allow the thrombi to be expressed from the common iliac arteries. The retrograde flow of blood from the iliac arteries at no time was vigorous. Following this procedure the tubing about the aorta was loosened sufficiently to allow the major portion of the embolus to be extruded. The rubber tubing was again used to compress the aorta and the lumen of the vessel was irrigated with heparin in saline solution. The intima was found to be raised up at one point and calcified on the anterior surface. After closure of the opening into the aorta and release of the constricting tubing, excellent pulsation could be felt on the left side as far as the external iliac artery. The right side was not completely exposed. The left common femoral artery was then exposed through a curved incision below the inguinal ligament, and was found to be occluded by a second embolus. After preliminary control of the superficial femoral, profunda, and common femoral arteries had been obtained, a transverse incision was made in the common femoral and the embolus and thrombi were removed. Marked spasm of the superficial femoral artery was noted, and no pulsation was detectable below the suture line. The abdominal incision was then closed. Following this procedure the femoral vessels were again inspected. A segment of polyethylene tubing was threaded through an 18 gauge needle, which had been inserted through the skin and subcutaneous tissues above the upper margin of the wound, and was then inserted through a stab wound in the left common femoral artery and forced upward into the iliac artery. This stab wound was made with a No. 11 blade in the center of a purse-string suture of No. 00000 Deknatel. A 30 gauge needle was attached to the polyethylene tubing and heparin in 5 per cent glucose solution, 100 milligrams in 500 cubic centimeters, was then injected into the artery during the remainder of the procedure at a rate of approximately 0.5 cubic centimeter per minute. After preliminary control of the component vessels, the common femoral artery was again opened but no further thrombi or emboli were found. The wall of the common femoral was extremely thick and in spasm. The incision in this artery was closed again with a continuous mattress, intima everting, suture of No. 00000 Deknatel. After closure of the wound the circulation on the left side appeared to be present down to the knee. The polyethylene tubing was attached to an intravenous apparatus and a continuous drip of heparin in glucose solution was continued throughout the night by raising the flask to a height of approximately 9 feet above the bed.

Eight hours after operation the patency of the polyethylene tubing could be demonstrated by the reflux of blood when the pressure in the injecting system was lowered. At this time it was clear that the circulation through the right lower extremity was sufficient for tissue nutrition, but on the left side the leg was ischemic below the knee and accordingly ice bags were applied to the left lower leg and foot. The intra-arterial heparin drip was continued for 3 days and the tubing was then removed.

On February 13 (3½ days after the start of regional heparinization of the left lower extremity), blood taken from the left antecubital vein showed a clotting time of 7 minutes and that taken simultaneously from the left iliac vein showed a clotting time of 17 minutes.

Four days after operation the patient had a sudden onset of pain and coldness of the right leg, extending from the hip to the toes. Examination disclosed definite color changes of the thigh and lower leg. She was again taken to the operating room, and under endotracheal anesthesia the abdomen was opened through a long right rectus muscle-splitting incision. A firm mass could be palpated at the bifurcation of the aorta extending down the right common iliac artery and for a distance of 2 centimeters into the internal iliac artery and for a distance of 4 centimeters below the inguinal ligament. A strong aortic pulse which extended down the left common iliac artery could be palpated. After preliminary control of the aorta and the external and internal iliac arteries, the right common iliac artery was opened and some loosely adherent thrombus was removed. The aorta was then opened at the bifurcation and a firmly adherent thrombus at the site of the previous suture was found. This thrombus was removed, and upon release of the aortic clamp a free flow of blood was obtained on the right side. The two incisions were then closed after irrigating the artery with heparin solution. The right femoral vessels were then exposed through a separate incision. After segments of rubber tubing had been placed about the femoral vessels and about the external iliac artery, this artery was opened through a short transverse incision at its mid-point. A long loosely adherent thrombus could be expressed at this opening. The incision was then closed in a similar fashion and upon release of the occluding rubber tubing the free flow of blood appeared in the common femoral artery. Actual pulsation extended only 1 centimeter distal to the inguinal ligament, and beyond this point the arteries remained in spasm. In an effort to increase the collateral pathways, the fourth lumbar sympathetic ganglion was excised on the right side. A segment of polyethylene tubing was then inserted into the common femoral artery on the right side and was passed up into the right external iliac artery to a distance of approximately 8 centimeters proximal to an inguinal ligament beyond which the tubing could not be passed. This polyethylene tubing was inserted through a stab wound made in the center of a previously placed pursestring suture of No. 00000 Deknatel. The pursestring suture was tied about the tubing, and a continuous injection of heparin in glucose solution, 100 milligrams in 500 cubic centimeters, was continued at the rate of 0.5 cubic centimeter per minute. The following morning the circulation had returned to the right leg, although the foot was still ischemic. At this time the patient showed evidence of a cerebral vascular accident with aphasia, which was of a temporary nature. That night she suddenly went into shock with signs of intraperitoneal hemorrhage and died the following morning.

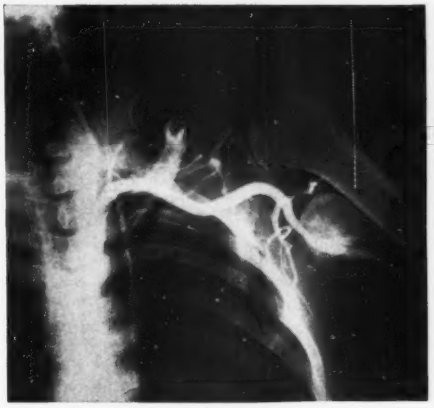

Fig. 5. Retrograde arteriogram in Case 5 illustrating aneurysm of second portion of left axillary artery.

Postmortem examination revealed a massive intraperitoneal hemorrhage, although the suture lines in the arteries were apparently intact. Although there were mural thrombi present at the sites of the incisions, only the left internal iliac artery was occluded by a thrombus. Both femorals, external iliac, and common iliac arteries were patent.

With regional heparinization it was possible to re-establish the patency of an artery which had been occluded by the lodgment of an embolus 3 and even 4 days previously.

CASE 5. A. C., Franklin Hospital No. 22295. A white male, aged 34 years, was admitted to the hospital on May 3, 1949, with a chief complaint of a pulsating mass in the left axilla. Two years prior to entry the patient had sustained a fracture of the left humerus with nonunion. One and one-half years before admission a bone graft with screws had been inserted into the upper end of the left humerus. The screws were removed 4 months before entry, and shortly thereafter he noticed a pulsating mass in the left axilla. Retrograde arteriography by means of injection of diodrast into the left brachial artery demonstrated an aneurysm which measured 4 by 3.5 centimeters arising just below the origin of the circumflex branches (Fig. 5). On the following day under general anesthesia the axillary artery was exposed distal to the pectoralis minor muscle. It was surrounded by a segment of rubber tubing and the brachial artery below the aneurysm was identified and surrounded by another segment of tubing. The proximal segment of rubber tubing was just distal to the point of origin of the subscapularis and circumflex branches. The cords of the brachial plexus were carefully freed from the surface of the aneurys-

mal sac and the axillary artery gradually dissected away from the sac to the point of communication. The opening was found to measure 1.5 centimeters in length and to occupy two-thirds of the circumference of the vessel. The sac was excised and a segment of arterial wall 2 millimeters in width surrounding the defect, which contained scar tissue, was excised in an elliptical fashion. The proximal and distal segments of the artery were then approximated and a transverse closure of the defect was effected by a continuous intima everting, mattress suture followed by a continuous over-and-over stitch. Before release of the rubber tubing, heparin solution, 20 milligrams in 100 cubic centimeters of saline, was injected through a 30 gauge needle into the axillary artery above the upper segment of rubber tubing. This injection was continued for a period of 10 minutes until the distal arterial segment had dilated and good pulsation was palpable in the brachial artery below the site of suture. The wound was then closed in layers. The patient was discharged from the hospital on the third postoperative day, and when the sutures were removed (2 weeks after operation) the radial pulse was normally present on the left side.

Regional heparinization was used in this case for a brief period following repair of the artery until there was dilatation of the distal arterial segment and a good volume flow of blood across the suture line.

SUMMARY

1. Regional heparinization has been carried out in a series of patients after the removal of emboli and after arterial repair following an injury or excision of an aneurysm.

2. The heparin solution has been injected either through a needle or through a segment of polyethylene tubing inserted into the artery directly above the suture line.

3. In 2 patients, after removal of emboli which had been lodged 1 and 3 days, the intra-arterial injection was continued for 19 hours and 3 days respectively. In the other patients the injection was made at the time when the operation was performed until the spasm of the distal arterial segment relaxed and good pulsatile flow was apparent beyond the suture line.

4. Regional heparinization is of value in the prevention of thrombosis at the suture line. The danger of hemorrhage from the wound is decreased by this form of administration of an anticoagulant.

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AN ATTEMPT TO EVALUATE THE RADICAL AND PALLIATIVE TREATMENT OF BREAST CARCINOMA

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UNDER what circumstances is the operation for the removal of a scirrhous tumor of the breast proper, and under what circumstances is it improper?" This question was asked by Sir Benjamin Brodie in the year 1865, more than 80 years ago. In the light of our present differences of opinion concerning the operability of certain carcinomatous lesions of the breast, we may truthfully say that Mr. Brodie's question is still very pertinent in the year 1949. In this discussion I shall consider some of the problems which daily present themselves to surgeons who are concerned with the choice of the best treatment of breast cancer.

INDICATIONS FOR THE RADICAL OPERATION

The results of surgical treatment depend upon the care with which patients are selected for operation. The more closely the patients are screened, the greater the number that may possibly be cured in the selected group. The rigid criteria of operability outlined by Haagensen and Stout (16), as presented below, would undoubtedly improve operative results.

Women of all age groups, who are in good enough general condition to run the risk of major surgery should be treated by radical mastectomy, except as follows:

1. When the carcinoma is one which developed during pregnancy or lactation.
2. When extensive edema of the skin over the breast is present.
3. When satellite nodules are present in the skin over the breast.
4. When intercostal or parasternal tumor nodules are present.
5. When there is edema of the arm.
6. When proved supraclavicular nodes are present.
7. When the carcinoma is the inflammatory type.
8. When distant metastases are demonstrated.
9. When any two, or more, of the following signs of locally advanced carcinoma are present: (a) ulceration of the skin; (b) edema of the skin of limited extent (less than one-third of the skin over the breast involved); (c) fixation of the tumor to the chest wall; (d) axillary lymph nodes measuring 2.5 centimeters or more in transverse diameter and proved to contain metastases by biopsy. (e) Fixation of axillary lymph nodes to the skin or to the deep structures of the axilla, and proved to contain metastases by biopsy.

Knowing the great variability of the natural growth of carcinoma, with its unpredictable tendency to remain local or to metastasize early in certain cases, the rules of operability must be somewhat flexible and tempered with seasoned judgment. When the best examination possible is made and no extension of the tumor is found beyond the area which may be removed by the radical operation, the patient should be given the benefit of the doubt and operated upon. This plan should be applied to all types of breast carcinoma, including the inflammatory type and those developing during lactation or pregnancy. If the criteria of operability of Haagensen and Stout are followed strictly, a small percentage of patients may be denied the possibility of a cure.

The slight difference of opinion expressed above does not detract from the value of the rules of Haagensen and Stout when applied in the teaching of young surgeons. On the contrary, young surgeons would do well to memorize the criteria of these authors and, with a few exceptions, apply them until further advancement is made in the treatment of breast cancer.

TECHNIQUE OF THE RADICAL OPERATION

Is there a standard technique for the radical breast operation? Brooks and Daniel have expressed the opinion that "There is no such thing as a radical operation for carcinoma of the breast as there is a Billroth II for carcinoma of the stomach," and "even Halsted (17 to 22) was somewhat confused as to what constitutes the operation bearing his name." Granting that these authors may be right in

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their opinions, the terms "Halsted operation" and "radical operation," have been used synonymously too long to be completely ignored. At risk of slight equivocation we might speak of the Halsted principle of the radical operation rather than the Halsted operation.

What type of skin incision should be used? How much skin over the breast should be removed? How much subcutaneous fat should be removed from the skin flaps? Should the pectoralis major be removed completely up to the clavicle? Should the anterior sheath of the rectus muscle be removed? Should the thoracodorsal and long thoracic nerves be preserved? Is excision of the axillary vein ever indicated? All these are questions which probably cannot be answered to the satisfaction of every surgeon. The opinions expressed below are offered for your consideration.

The type of skin incision selected should be the one most suited to the individual case. The location and size of the tumor, the size and shape of the breast, and the obesity of the patient, may all be factors influencing the choice of incision. Dr. Bevan, whom we are honoring tonight, stated in 1930 that "No fixed set incision should be adopted. The incision should be planned, and can be planned, so that in almost all cases a skin closure can be made without tension, making skin grafting seldom necessary." With rare exceptions one of the incisions illustrated in Figure 1 is satisfactory. These incisions do not cross the axilla and, therefore, reduce to a minimum any scarring which might limit arm function.

Judging from written reports it is too much to ask all surgeons to agree upon the extent of skin to be removed with the breast. There are ardent followers of Halsted who remove large areas of skin and close the defect with skin grafts, and equally as ardent followers of Sampson Handley who advocate extensive removal of fascia with primary skin closure. Halsted was clear in the statement of his belief that a large area of skin should be removed requiring a skin graft. He taught that "to attempt to close the breast wound more or less regularly by any plastic method is hazardous, and, in my opinion, to be vigorously discountenanced." Lewis and Reinhoff seconded Halsted's teaching when they expressed the opinion that "the operator cannot be held responsible for undiscoverable metastases, either regional or remote, but should be held to account for a local recurrence." According to Haagensen (14) the surgeon "cannot escape responsibility for the button-like recurrent skin nodules which are apt to appear along the scar line when an inadequate area of skin is removed." Handley believed that his method of removing a very wide area of deep fascia and a less wide area of skin to permit primary skin closure, produced better results than the removal of less fascia and more skin. Conway and Neumann, after a study of their results, recommended more radical excision of skin. White makes a statement, which seems to be substantiated by a study of the literature, that with either the Halsted or Handley approach, there is a high incidence of local recurrence, and there is no proof that one method is better than the other. Rodman's low incidence of 2.2 per cent of local recurrences after radical mastectomy with plastic closure, while encouraging, cannot be accepted as anywhere near the average of local recurrences with any type of closure. Oliver and Sugarbaker have reasoned that "wide skin excision, although it might conceivably diminish the clinical manifestations of skin recurrence, would not, in our opinion, improve the 5 year survival of patients." The incidence of skin recurrence is undoubtedly influenced by the extent of metastatic involvement of the axillary lymph nodes. Warren and Tompkins have presented conclusive evidence that recurrences in the operative scar increase with the extent of the disease in the axillary lymph nodes. These authors suggest that local recurrences are of the nature of metastases or extensions, rather than implants.

If we accept Haagensen's conclusion that carcinoma cells are implanted by the surgeon's instruments, thorough lavage and irrigation of the wound with physiologic sodium chloride solution are indicated before the skin is sutured. In 1866, Samuel D. Gross recognized the importance of removing all particles of tumor from the operative wound and expressed himself as follows: "Before the parts are approximated, the wounded structures are examined with the greatest care, in order that

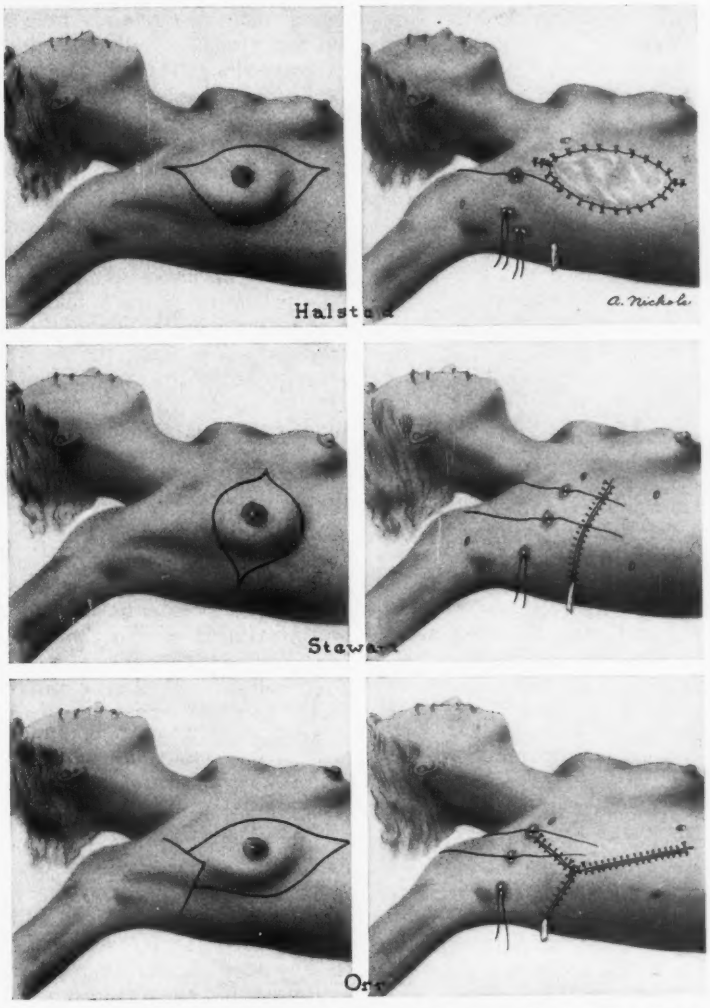

Fig. 1. Skin incisions and wound closures suitable for nearly all radical breast operations. Dead space is obliterated and the axillary vessels are covered by approximating the skin and chest wall muscles high in the axillary sulcus with mattress sutures of silk.

not the slightest particle of the morbid substance may be left. Indeed, the very atmosphere of the disease should be removed."

To minimize local recurrences after the radical operation, it seems logical to believe that the thoroughness of the axillary dissection may be as important as the extent of skin removed. Written evidence is not sufficient to condemn or approve the removal of large areas of skin with skin grafting, or lesser areas of skin with primary wound closure, as a part of the radical breast operation. By avoiding a fixed idea attitude, and by individualizing the technique of operation to suit the existing condition, a solution to the problem may be approached.

Removal of the clavicular portion of the pectoralis major muscle is not necessary for good axillary exposure. Leaving a narrow strip of pectoral muscle attached to the clavicle is not of great importance and could hardly influence the result of a radical operation.

A very thin layer of fat may be left attached to the skin flaps of a breast operation. It is hardly necessary to trim the fat so close that the skin flaps are essentially full thickness grafts.

Removal of the fascia of the thoracic portion of the rectus muscle is indicated when axillary metastases are present, when the tumor is located in the lower half of the breast, or when there is any doubt about the extent of the primary growth. Since excision of the rectus fascia requires but a few moments and does not increase the hazard or mutilation of the operation, this fascia may, with good judgment, be removed routinely.

The thoracodorsal and long thoracic nerves should generally be preserved. If involved lymph nodes are found along the former nerve, it should be removed. The long thoracic nerve lies against the chest wall and can be preserved without fear of changing the result of the radical operation.

MacDonald recommended the routine removal of the axillary vein as part of the radical operation. Trimble advised resection of this vein if it is found invaded by metastastic growth. This author stated that no harm will follow resection of the vein. The advice of Trimble is sensible and acceptable.

Probably of more importance than any of the above points in technique is a painstakingly complete dissection of the axilla.

BIOPSY

Will biopsy and operation disseminate tumor cells? At the beginning of the Christian Era, Celsus made the statement that "There is not so great danger of cancer, unless it be irritated by the imprudence of the physician." In 1898 Halsted remarked that "Tumors should never be harpooned, nor should pieces ever be removed for diagnostic purposes."

There is a wide difference of opinion among surgeons and pathologists concerning the danger of biopsy. Certainly precautions should be taken against cell dissemination when a biopsy is done. If the tumor is small it should be excised completely. If the tumor is large the biopsy wound should be packed and closed and the skin should be prepared again for operation. Gloves and instruments which have been used should be changed. There is unmistakable evidence that cancer cells can be spread by operation. White reported transplantation of cancer from the breast to a donor site on the thigh when taking a skin graft. Haagensen stated that recurrent skin nodules, which develop along the scar line when an inadequate area of skin is removed, develop beyond all doubt, from carcinoma cells implanted by the surgeon's instruments as he manipulates or sutures the edges of the wound. Cutting through cancer invaded tissue does not mean that the cells are necessarily disseminated by operation, but it is undoubtedly true that cells do grow locally in such instances when not completely removed.

Biopsy is an essential part of the diagnosis and treatment of many breast cancers and cannot be discarded because of the possible danger of cancer cell dissemination. Biopsies should be made with great care and definitive treatment should follow as soon as possible if cancer is found.

POSTOPERATIVE COMPLICATIONS

The mortality of the radical operation rarely exceeds 2 per cent. The reason for the low mortality is very probably due to the modern method of replacing blood loss during the operation. Infection is infrequent. Delayed healing may occur as a result of necrosis of skin flaps, but the loss of skin is rarely extensive enough to require skin grafting. Collection of serum beneath skin flaps may delay healing and produce fibrosis. Such collections of serum can be reduced to a minimum by proper drainage through small stab wounds in the flaps, approximation of flaps and chest wall with sutures, and pressure dressings. When serum collects beneath flaps it should be evacuated promptly by stab wounds or by aspiration.

Limitation of motion at the shoulder may result in some cases due to fibrosis and occa-

TABLE I.—ANALYSIS OF THE TREATMENT OF 422 CASES OF BREAST CARCINOMA (1924 TO 1944)

	Cases	Per cent
Total number of radical operations.....	208	49.3
Total number of subradical operations...	79	18.7
Total number of simple mastectomies....	45	10.7
	332	78.7
Total number not operated upon.....	90	21.3
	422	100.0

sionally arthritis of the shoulder joint. This complication can be reduced in frequency by encouraging early motion of the shoulder and use of the arm.

Postoperative edema of the arm often follows the radical operation. The edema is frequently confined to the upper arm and is relatively unimportant. Extensive edema, involving the entire arm and hand may be very inconvenient, distressing to the patient, and sometimes disabling. Since various operations designed to diminish edema of the arm by increasing the lymph drainage usually have been of questionable value, prevention of edema should be the surgeon's objective. Edema may be prevented in some measure by carefully covering the axillary vessels and by obliteration of all dead spaces with the skin flaps. Halsted emphasized this point in 1913. He sutured the skin to the intercostal muscles to cover the axillary vessels after wide removal of the breast with its overlying skin (Fig. 2).

Figure 1 shows mattress sutures used to suture the skin flaps to the intercostal muscles. By this method the axillary vessels are covered and the axillary sulcus is obliterated.

Fig. 2. Fold of skin stitched to underlying muscles at margin of area to be grafted to cover axillary vessels (Halsted, 21).

RESULTS OF TREATMENT OF AUTHOR'S CASES

Of 422 hospital cases of carcinoma of the breast in patients admitted to the University of Kansas Medical Center from 1924 to 1944, 332 were operated upon. Of this number 17 were not traced, leaving 315 cases for analysis. Approximately 75 per cent of the patients were operated upon by the author and the remainder by eight other surgeons (Table I).

The results of surgical treatment are shown in Table II. The grouping conforms to that suggested by Steinthal, and is based upon the pathological rather than the clinical examination, except in cases of a simple mastectomy. The operations are divided into radical, subradical, and simple mastectomy. The term subradical has been used for operations in which the breast, axillary contents,and pectoralis minor muscle have been removed, leaving the pectoralis major muscle intact.

The radical operation was done in 29 of group III cases. Since no patient lived as long as 5 years, the radical operation must be considered contraindicated in this group.

The results of the subradical operation were superior to those of the radical operation. The

TABLE II.—RESULTS OF OPERATION IN 315 TRACED CASES (17 CASES WERE NOT TRACED)

	Group	No.	Lived 5 to 9 yrs.		Lived 10 to 19 yrs.	
			No.	Per cent	No.	Per cent
Radical operation	1	77	50	64.9	19	24.6
	2	89	24	26.9	8	8.9
	3	29	0	0.0	0	0.0
Subradical operation	1	40	34	85.0	10	25.0
	2	36	15	41.6	0	0.0
	3	0	0	0.0	0	0.0
Simple mastectomy	1	13	8	61.5	2	15.3
	2	2	0	0.0	0	0.0
	3	29	0	0.0	0	0.0

selection of cases for operation accounts for the better results. In this group patients were selected with minimal lesions after a biopsy had been studied. Many of the patients had carcinoma arising in ducts with beginning invasion only. What these results would have been had the radical operation been done, one can but speculate.

The cases in the small group of simple mastectomies were selected because of minimal lesions, ages of patients, or ulcerating lesions. Those patients having no clinical evidence of axillary metastases were placed in group I. The results in group I were far better than our expectations, even though some patients dying of other diseases are included in these calculations.

Approximately 200 of the 332 patients operated upon received preoperative or postoperative x-ray therapy, or both. The number of patients is too small and the follow-up records are too incomplete to judge the merits of irradiation therapy in this series. However, it is my impression and the impression of the radiologist, that life has been prolonged in some patients by postoperative irradiation. There were 7 postoperative deaths, or 2.1 per cent, in this series of 332 cases. Twenty patients had carcinoma of both breasts, a percentage of 4.7.

Of the 90 patients not treated by surgery, some were treated by irradiation, some refused treatment, and others were so far advanced that treatment was not advised.

IRRADIATION THERAPY

That irradiation therapy is of value in the treatment of advanced carcinoma to relieve suffering and prolong life, has been accepted by almost everyone interested in the subject. No such definite statement can be made concerning preoperative and postoperative irradiation. Goin stated the case clearly when he said that "the debate is almost entirely as to the extent to which irradiation should augment or even replace surgery in the treatment of the disease, and indecision is expressed even by those of the widest experience." Pfahler and Keefer decided that recorded statistics do not justify any definite conclusion concerning the value of preoperative irradiation. But it is their opinion that operative results can be improved by preoperative or postoperative roentgen therapy, or by a combination of the two. These authors report a 10 per cent increase in 5 year survivals after treatment by irradiation postoperatively. Lenz reported that routine prophylactic roentgen therapy has been discontinued at the Presbyterian Hospital in New York. McGraw's (29) results were inclusive. Gordon-Taylor expressed strong opposition to "ancillary radiation" in groups I and II. A reasonable viewpoint recorded recently by Sir Cecil Wakeley that the treatment of carcinoma of the breast is a radiosurgical problem, and the parts played by x-ray and surgery must be taken into consideration before embarking upon either, will probably meet with the approval of surgeons in general. It is Wakeley's further opinion that x-ray therapy is still in the process of evolution, and the relative merits of the different irradiation techniques are undecided.

A rather extreme viewpoint in favor of irradiation therapy has been expressed by McWhirter of the Royal Infirmary of Edinburgh. This author advised simple mastectomy and postoperative roentgen therapy (of a high standard) as a method of treatment of breast cancer superior to radical mastectomy. He reported 56 per cent of 5 year survivals in all "operable" cases.

With abundant evidence recorded that irradiation will devitalize or destroy breast cancer cells, one cannot logically say that preoperative and postoperative therapy is of no value. According to Pfahler and Keefer there is both theoretical and biological evidence favoring preoperative irradiation, and these authors have presented evidence that normal tissues are less receptive to implantation of cancer cells after preoperative roentgen therapy.

Any surgeon who has watched the favorable progress of inoperable cases of breast cancer after patients have been treated by a competent radiologist, must, in all fairness, reason that cancer cells existing beyond, or remaining in the operative field after the radical operation, may be devitalized or destroyed by the roentgen rays. If this viewpoint is accepted, postoperative irradiation is indicated in all cases in which there is a reasonable possibility

that cancer has not been removed completely by operation.

At present, it is the policy at the University of Kansas Medical Center to give postoperative irradiation in all cases in which metastases to the axilla have been found by the pathologist. In group I (so classified after the pathologist fails to find metastases in the axillary nodes) irradiation therapy is not advised. To subject a patient to the possibility of skin burns, increased fibrosis of the axillary area, and fibrosis of the lung, seems unwarranted when evidence of the spread of cancer cannot be found.

SURGICAL AND IRRADIATION CASTRATION

Since estrogens have been shown to increase the growth of breast cancer experimentally, and their therapeutic use to increase the rapidity of cancer growth, it is reasonable to believe that castration may be of value in the treatment of patients before the menopause.

Transient benefit may be expected by castration in some cases. Farrow estimated that beneficial results may be obtained in about one-third of the cases. Patients with good results may have relief from pain, improvement of appetite and strength, and sometimes regression of metastases, especially metastases in bone.

When recommending castration in women, one must recognize that possible bad effects of the treatment may be both physical and psychological. Since castration is never curative, and is only temporarily beneficial, routine castration in all patients of premenopausal age with breast cancer should not be recommended. Such treatment should be reserved for patients with advanced disease.

Castration to prevent pregnancy in a woman who has been operated upon for cancer is hardly warranted unless there is good reason to believe that her survival time is to be short. I doubt if there are many good reasons for depriving a woman of motherhood even though she may eventually die of cancer.

USE OF SEX HORMONES

Treatment of breast carcinoma with sex hormones may be palliative, but never curative. The best results have been obtained with testosterone. When given in advanced cases in relatively high dosage, favorable and worthwhile palliation is obtained in some cases. Adair (1) reviewed the entire subject of testosterone therapy and concluded that "the influence of testosterone on growth processes of mammary carcinoma is so profound and striking, even though frequently disappointing, that clinical and metabolic studies should be pursued by investigators with the greatest vigor." More recently (August, 1949) Adair and associates (2) summarized their study of 70 patients treated with estrogens and androgens. They reported objective improvement in 19 per cent of patients with skeletal metastases, and 15 per cent with extraskeletal metastases treated with testosterone propionate.

In certain cases of advanced carcinoma treated with testosterone, life may be prolonged, pain relieved, disability reduced, appetite increased, weight gained, sleep made possible without narcotics, and a general feeling of hope and well-being may be renewed.

The disagreeable features of the treatment have been hirsutism, voice change, acne, enlargement of the clitoris, increased libido, edema, and hypercalcemia.

Estrogens may be expected to benefit some patients with advanced carcinoma who have passed the menopause. Nathanson and coworkers advise that estrogens should be used only in patients at least 5 years following cessation of uterine bleeding, regardless of chronological age. These authors report that 60 per cent of patients treated with estrogens, and 62 per cent treated with testosterone showed subjective improvement.

Our experience with 12 cases at the University of Kansas Medical Center, treated under the direction of Dr. Tice, has been encouraging. All of the patients had metastases. Eight patients complained of pain. Five were treated with 100 milligram doses of testosterone three times per week, and four with 200 milligram three times per week. All were relieved of pain but no evidence of healing of bone metastases was noted. Three patients treated with stilbesterol did not show any improvement. It is the opinion of Tice and his associates that life is not appreciably prolonged by testosterone treatment. Such treat-

TABLE III.—SOME RESULTS OF RADICAL OPERATION FOR CARCINOMA OF THE BREAST IN THE LAST TEN YEARS

Author	Yr.	Group I without axillary metastases			Group II with axillary metastases		
		No.	5 year survivals Per cent	10year survivals Per cent	No.	5 year survivals Per cent	10year survivals Per cent
Brooks and Daniel	40	12	91.6		60	26.7	
Haagensen and Stout (15)	42	237	61.2		385	21.0	
Simmons	42	42	73.0	70.0	99	30.0	18.0
Guthrie	43		65.5	40.9		23.0	9.8
Warren and Tompkins	43	81	85.0		90	38.0	
Harrington	46	2427	75.7	57.9	3728	30.4	16.4
McGraw (28)	47	161	64.0		251	29.6	
Gordon-Taylor	48	113		84.0	204		29.4
Everbach	49	93	82.0		150	33.0	
Orr	49	77	64.9	24.6	89	26.9	8.9

ment is of definite palliative value, particularly when combined with x-ray therapy.

DISCUSSION

The value of surgical treatment of breast carcinoma cannot be estimated accurately. It is obvious that the more carefully patients are selected for operation, the better will be the results. But if selection is carried to an extreme, some patients may be denied operation which would place them in the incurable group suitable only for palliative therapy. Fewer patients treated by operation and a greater number treated by palliation, will not contribute much to the improvement of the over-all problem of breast cancer.

Some of the results of the radical operation recorded in the last 10 years are listed in Table III.

Grading of breast carcinoma to estimate the prognosis has not proved of great importance. Warren and Tompkins state that histological grading was not found to be significant in their laboratory. The factors which influence prognosis are, the extent of the tumor, the thoroughness of its removal, and the care with which the tissue is studied by the pathologist. Warren and Tompkins found that when less than half of the axillary nodes showed metastases, the 5 year survivals were 68 per cent, when more than half were involved, the survival rate was 38 per cent, and when all nodes contained cancer, only 19 per cent were alive at the end of 5 years. That much depends upon the pathologist is confirmed by the study of axillary lymph nodes made by Saphir and Amromin. These authors discovered, by making serial sections of nodes in 30 cases already routinely reported in their department of pathology, that an additional 33 per cent contained cancer.

Is there any place for the subradical operation in the treatment of breast cancer? Forty years ago (1907) Greenough and associates reported better results with the incomplete, than with the complete, operation. With the incomplete operation 25.9 per cent were free of recurrence, compared with 16 per cent with the complete operation. The better results with the incomplete operation are explained by a careful selection of cases. My results reported here are better with the subradical than with the radical operation. But one could not conclude with assurance that the radical operation would not have produced the better results if used in all cases. The only possible excuse for doing a subradical operation is that it is somewhat less dangerous, less mutilating, and produces less disability. To teach young surgeons to do anything less than the radical operation would probably be considered heresy by many experienced surgeons. Certainly any such teaching should be carefully qualified by a full explanation of its possible dangers. The most skillful surgeon cannot always detect metastases in the axillary nodes at the operating table, and certainly no patient having demonstrable cancer in nodes should be treated by the subradical operation.

Will increasingly radical surgery produce better results in the treatment of breast cancer? We are now in an era of radical surgery. New and extended techniques may improve results. Gordon-Taylor has recently (1948) added removal of the anterior mediastinal glands and internal mammary artery to his technique of the radical operation. Pickrell and coworkers have excised large portions of

the chest wall for recurrent breast cancer. These reports show the trend of the times toward more radical breast surgery. No surgery can be too radical if it will save life without misery, but we cannot, at present, look far enough into the future to dispel the doubt that extensive radical procedures will produce better results than x-ray therapy in what are now generally considered incurable cases.

CONCLUSIONS

All types of therapy for carcinoma of the breast, except surgical, must be considered palliative. Since no one knows the percentage of cures that may be expected from surgical therapy, the term "survivals" is more in keeping with our present knowledge of the natural history of the disease.

If we accept irradiation as valuable treatment for inoperable cancer of the breast, it would be illogical to assume that such treatment would be without merit as an adjunct to surgical therapy.

Palliative results of castration and hormone therapy have been of sufficient value in the management of advanced carcinoma of the breast to justify their use in selected cases.

Possibly more radical surgery in the future may salvage a very small percentage of breast carcinomas now considered incurable.

It is very evident that there are many problems relating to the treatment of carcinoma of the breast which remain unsolved. To champion one method of treatment or technique of operation to the exclusion of all others may smack of dogmatism, and dogmatism never does much toward the solving of scientific problems. Oliver Wendell Holmes, who was acutely aware of the weaknesses and foibles of the medical profession, once said that, "Scientific knowledge, even in the most modest persons, has mingled with it something which partakes of insolence," and Martin Fischer warned that "the printed page is not the truth nailed down, but the author."

We must keep an open and discriminating mind concerning the many opinions extant, and look with a discerning eye upon future conclusions which may lack basic truths. Opinions should be respected, but should not be mistaken for facts.

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THE SIGNIFICANCE OF DIFFERENT METHODS FOR PROTHROMBIN ESTIMATION AND THEIR RELATIVE VALUES

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THE estimation of plasma prothrombin is clinically useful in the diagnosis and treatment of certain hemorrhagic tendencies, in the measure of liver function, and in the control of anticoagulant therapy. Its widespread and increasing use, both clinically and in research, makes it an important tool in the hands of the physician, but the present confusion in the methods for measuring prothrombin has detracted considerably from the usefulness of the tool. It is the purpose of this paper to examine the presently available methods and to try to interpret their meaning.

THEORY OF BLOOD COAGULATION

The methods for estimating prothrombin are, at the present time, bio-assays. Prothrombin can be measured only by its ability to form thrombin and successively by the ability of thrombin to clot fibrinogen. Since prothrombin is a glycoprotein without characteristic chemical groups in the molecule (18), it is not likely that a chemical method for measuring it will soon be discovered. Therefore, in order to understand methods for estimating prothrombin, it is necessary to understand the mechanism by which blood clots. In 1904 Morawitz postulated that this process occurs in two stages involving the interaction of four factors. In the first stage, prothrombin in the presence of thromboplastin and calcium is converted to thrombin. In the second stage, thrombin acts on fibrinogen, to convert it to the relatively insoluble fibrin which is the clot. This theory stood without significant alteration until 1944 when Owren (10) added another factor which he called factor V. This factor serves to accelerate the conversion of prothrombin to thrombin, and he demonstrated that it was essential to the normal physiologic clotting mechanism. Working independently, two other groups of investigators, namely Fantl and Nance and Ware, Guest, and Seegers (22), also discovered the accelerator factor, the latter group demonstrating the mechanism of its action and naming it accelerator globulin or Ac-globulin. Earlier, Quick (14) found that mixing stored plasma and dicumarolized plasma, both of which had prolonged prothrombin times, restored that time to normal. On this evidence he postulated that there were two components of prothrombin, one (component A) being lost in stored plasma, and the second (component B) disappearing from the plasma in a patient receiving dicumarol. There is, however, little evidence to support this concept of more than one prothrombin, and Quick later substituted the term labile factor for component A (15). It is generally considered to be identical to factor V and Ac-globulin. It should be recalled at this point that as early as 1939 Warner, Brinkhous, and Smith (24) demonstrated that the conversion rate of prothrombin varies widely in different species and not infrequently within the same species. In the light of recent studies (5) the accelerator factor is at least in part responsible for such variation.

The interaction of the above known coagulation factors may be opposed or altered by certain known anticoagulation factors—antithrombin (7, 19), antithromboplastin (7, 17, 20, 21) and heparin. At this point the mechanism of their action need not be considered.

Other factors influencing the coagulation process are the *p*H values and temperature

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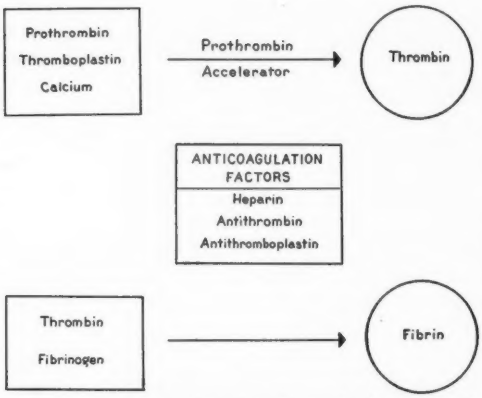

Fig. 1. This chart represents the mechanism of blood coagulation. According to the generally accepted theory, blood coagulates in two stages. In the first phase prothrombin in the presence of thromboplastin, calcium and the prothrombin accelerator (factor V, Ac-globulin, labile factor) is converted to thrombin. In the second stage thrombin converts fibrinogen to the relatively insoluble fibrin. Present in varying amounts are the known anticoagulation factors, heparin, antithrombin and antithromboplastin, influencing individually or collectively the clotting mechanism. Control of these factors is important in assaying for prothrombin.

variations. It is possible also that the plasma colloids other than those which are directly involved serve to stabilize the coagulation mechanism.

Thus, the clotting of blood is a relatively well balanced mechanism which may be disturbed by variations in one or more of either the coagulation or anticoagulation factors.

PROTHROMBIN METHODS

At the present time there are a number of methods employed clinically and experimentally for measuring prothrombin, most of them being based on the one stage technique described originally by Quick, Stanley-Brown, and Bancroft (16), or the two stage method of Warner, Brinkhous, and Smith (25).

One stage method. Quick and his associates postulated that the clotting time of recalcified, oxalated plasma to which had been added an excess of thromboplastin was a function of the amount of prothrombin in the plasma. The temperature of the reaction was controlled at 37 degrees Centigrade, calcium concentration was optimal, the plasma colloids served to stabilize the reaction, and the plasma itself served to maintain the p_H within a satisfactory range for the optimal clotting of blood. Uncontrolled, however, were fibrinogen, prothrombin accelerator (factor V, Ac-globulin, labile factor) and the various anticoagulation factors, namely antithrombin, antithromboplastin, and heparin. Also, in the one stage test the two phases of the clotting process were allowed to proceed concurrently in the same test tube. Recently, Flynn and Standley have shown that the end point in the one stage test may be reached when as little as 40 per cent of the available prothrombin has been converted to thrombin. Thus, a plasma containing 40 per cent of the normal amount of prothrombin might give a 100 per cent prothrombin estimate by this method. Such an error might also be brought about or be exaggerated by variations in one or more of the other uncontrolled factors.

In an attempt to obviate some of these variables and thus render it a more accurate prothrombin measure, numerous modifications of the one stage test have been developed. One of the most commonly used is that of Link and his associates (1), who found that diluting whole plasma to 12.5 per cent of normal resulted in a more sensitive measure of the varying prothrombin levels. Antithrombin (7, 25) and antithromboplastin (7, 21) are particularly sensitive to dilution and rendering of them ineffectual may be in part responsible for such findings. Owren (10, 11), by removing the prothrombin from beef plasma and fortifying such stored plasma with factor V (Ac-globulin), has eliminated certain of the variables in the one stage method and reduced the significance of others. In diluting the plasma to be tested to 10 per cent of normal he eliminates antithrombin and antithromboplastin as significant factors. Ziffren, Owen, Hoffman, and Smith simplified the one stage test by adding thromboplastin to carefully drawn whole blood at the patient's bedside (hence the name "bedside method") and compared unknown blood samples with control bloods. However, in that it ignores the fundamental mechanism by which blood clots, the one stage test must be considered a measure of factors other than and in addition to prothrombin, and is really a measure of the

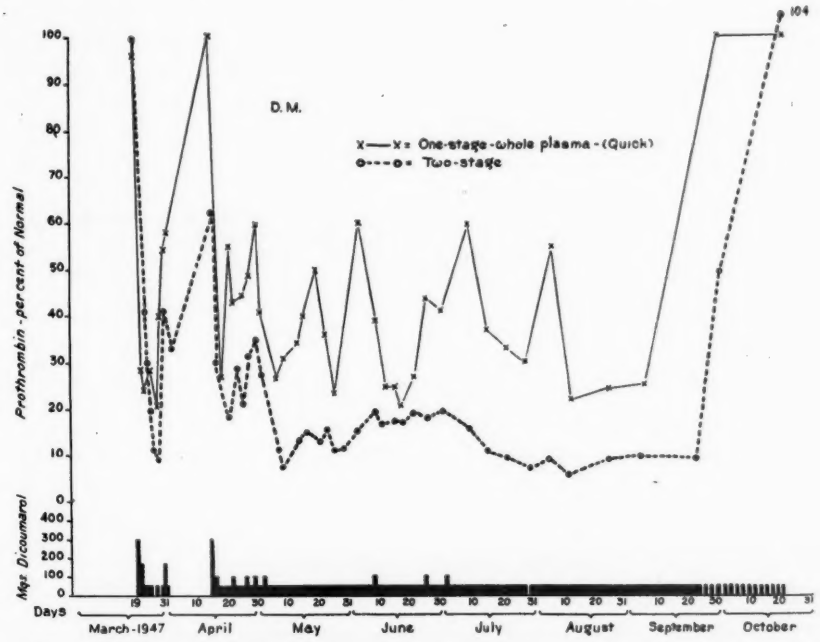

Fig. 2. This chart represents the comparative one stage and two stage prothrombin levels of a patient receiving dicumarol for thrombophlebitis. He left the hospital after 12 days and therapy was discontinued. Symptoms recurred 2 weeks later and therapy was reinstituted. Note the wide variations between the results of the two methods. According to the two stage test the prothrombin was well controlled on about 50 milligrams of dicumarol daily. The one stage, however, showed wide variations. Had the doses of dicumarol been controlled by the latter, the patient at several points would have been given larger doses and the prothrombin depressed to bleeding levels. On the other hand, on the several occasions when the prothrombin was 10 per cent or below according to the two stage, the one stage test, a summation of the clotting factors, registered a higher estimate, indicating that factors compensating for a low prothrombin would prevent bleeding. This patient had no bleeding at any time.

over-all clotting activity of the blood under certain specific conditions. Since it is often more important to know this than to know the level of a single factor, it is a valuable test.

Two stage method. By allowing the prothrombin conversion to go to completion and then in a second step to let the thrombin thus formed act on a standardized fibrinogen solution, Warner, Brinkhous, and Smith (25) eliminated a number of the variables present in the one stage test. The conversion rate of prothrombin was no longer an important factor. In addition, antithrombin and antithromboplastin were rendered ineffectual by dilution, a standard fibrinogen solution was used, the *p*H was controlled by a buffer, and acacia, a colloid, was added further to stabilize the reaction. Later, Seegers (23) and his associates added Ac-globulin which served further to assure complete conversion of the measurable prothrombin.

SIGNIFICANCE OF THE TWO METHODS

At the present time the two stage method is the most accurate measure for prothrombin. The chief objection to it is that it is difficult to perform, and this objection is valid to a certain extent. The reagents and equipment required for carrying it out are certainly more complicated than those for the one stage test, and the time required for doing a single test is longer. Once the required setup is obtained, however, the performance of the test is neither difficult nor excessively time consuming.

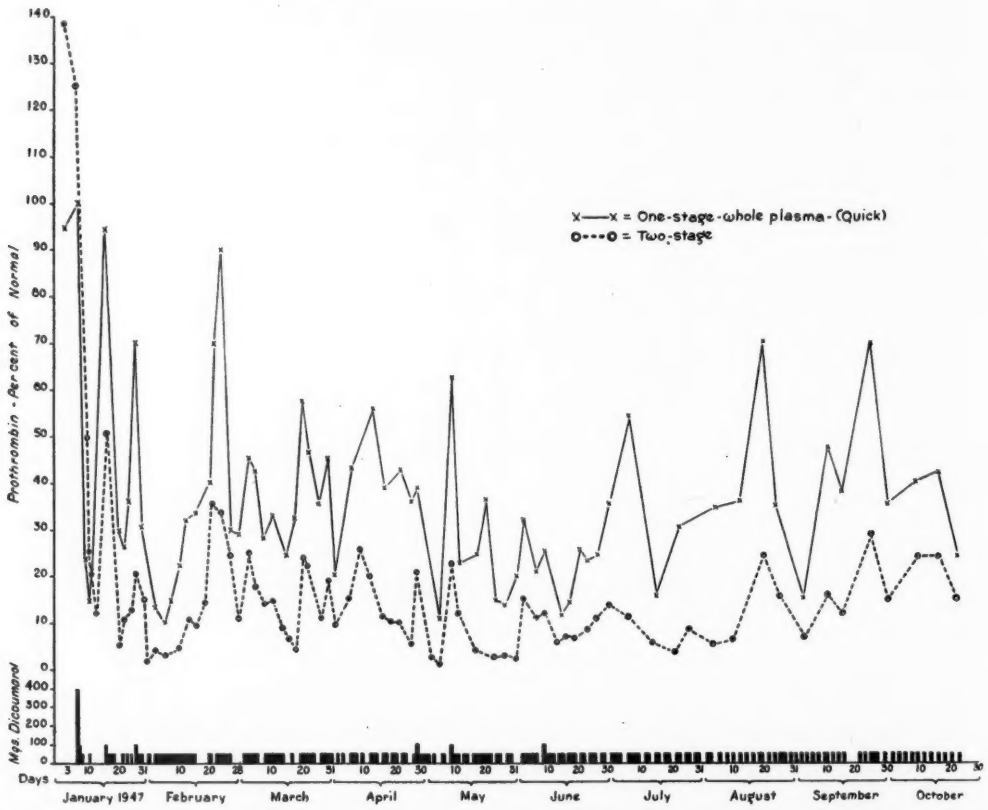

Fig. 3. Prothrombin levels, one stage and two stage, of a patient receiving dicumarol over a 10 month period. Originally, therapy was started for thrombophlebitis, and because she felt the symptoms of her multiple sclerosis were improved, her physician continued it over a period of time. She was treated as an outpatient after the first few weeks of therapy. Note the wide variations between the one stage and two stage prothrombin estimates.

Whereas, the two stage test is a more accurate measure of the available prothrombin, the one stage is a measure of the activity of a number of factors, both coagulation and anticoagulation. It is a more accurate gauge of the likelihood of bleeding in a patient than is the two stage test. It has been my experience, in the study of more than 350 patients on dicumarol therapy that the plasma prothrombin may drop to below 10 per cent without evidence of bleeding. Of those 350 patients, 109 at one time or another during therapy had a prothrombin level below 10 per cent, and of these 35 developed bleeding in some form. Other factors may compensate for a prothrombin deficiency, thus acting as a safeguard, and this safety factor will be registered by the one stage test. A plasma containing 5 per cent prothrombin by the two stage test will usually register 15 to 30 per cent or more by the one stage method (Figs. 2 and 3). By the same token, these other factors varying from day to day may be responsible for false prothrombin levels as measured by the one stage test (Figs. 2 and 3).

COMPARISON AND THE TWO METHODS

One naturally is interested in a comparison of the results of the two methods. My associates and I have run in parallel the two

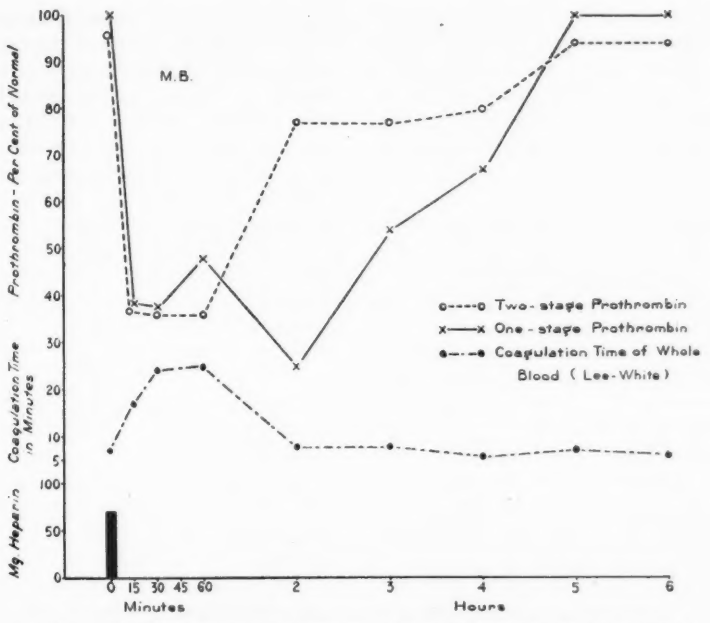

Fig. 4. This chart represents the response of the clotting mechanism (as reflected by prothrombin levels and coagulation time of whole blood) to 50 milligrams of heparin injected intravenously. Note that the coagulation time (Lee-White) of whole blood is prolonged for 1 hour, and by the end of 2 hours has returned to normal. The prothrombin estimate according to the two stage method has returned toward normal by the end of 2 hours, but remains below the preheparin level beyond 4 hours. The one stage test, however, which leaves as variables several factors influenced by heparin, shows an appreciable effect for as long as 3 hours, and return to normal is delayed to between 4 and 5 hours. The one stage is used in our laboratory as a control for heparin therapy.

stage test and the one stage method in over 3,000 instances. In most of these, the one stage test has been the original technique described by Quick and his associates (16), but we have also used plasma diluted to 12.5 and 5 per cent of normal, the "bedside method" in which thromboplastin is added to carefully drawn fresh whole blood (27), and we have had a limited experience with Owren's one stage method, using beef plasma from which prothrombin has been removed (10, 11).

In some instances, the results of the one stage and two stage tests will be parallel, the one stage usually being higher in its prothrombin estimate than the two stage method (8, 9). In the same patient, however, there will be wide variations in this difference from day to day, undoubtedly as a result of variations in one or more of the factors mentioned earlier. This is true of all one stage techniques used in our laboratory. Owren, who has had considerably more experience with his own technique than we have, states that it gives results closely paralleling those of the two stage method (13).

USEFULNESS OF THE TWO METHODS

It would seem to follow that the most accurate of the methods for estimating prothrombin would be the most valuable one in all instances. This, however, is not necessarily true. Rather, an understanding of what each test represents will provide for its proper application and allow a more accurate interpretation of its results. In some patients such as those with obstructive jaundice, the chief

concern of the surgeon is whether or not the patient will bleed during or following surgery, and in such cases the one stage method is a better estimate of the safety factor than is the two stage. This is generally true in all conditions in which information is desired as to the likelihood of bleeding from a prothrombin deficiency.

As an estimate of liver function both methods are of value. The two stage method, being a more sensitive reflection of changes in prothrombin, may show degrees of liver damage not registered by the one stage test. It should be remembered that the prothrombin level is of value as a liver function test only after adequate amounts of vitamin K have been made available to the liver (6).

In the control of anticoagulant therapy the prothrombin estimation may be used as a measure of the effect of both heparin and dicumarol. Heparin alters the coagulation mechanism in several ways, namely: (1) it interferes with the conversion of prothrombin to thrombin (7); (2) it lessens the tendency of platelets to agglutinate (26); (3) it catalyzes the antithrombic activity of plasma (19); and (4) it may inhibit the activity of factor V (13). We have found the one stage method to be a more sensitive measure of heparin effect than the more commonly used coagulation time of whole blood (Fig. 4). Since the one stage method leaves uncontrolled more of the above mentioned factors which may be affected by heparin, it is more useful in heparin therapy than is the two stage method. We have found that a dosage of heparin which will reduce the prothrombin by the one stage method to 35 per cent of normal is clinically effective when given intravenously every 4 hours. Its effect will persist for from 4 to 6 hours in most instances. It must be remembered that in combined heparin and dicumarol therapy blood taken for a prothrombin level to measure dicumarol effect must be drawn after the effect of heparin has been dissipated.

In dicumarol therapy, efforts are directed toward the control of the single factor, prothrombin, and the two stage method is the one of choice. Because of the uncontrolled factors in the one stage test, its estimate may vary from day to day from the actual prothrombin level, and too much or too little dicumarol may be given. With the use of the two stage method the prothrombin of most patients may be kept near the generally accepted 10 to 30 per cent bracket over an indefinite period of time, and they may be safely and effectively carried as outpatients. The one stage test is of value, however, as a measure of the safety factor. When the two stage shows a level below 10 per cent, bleeding is unlikely if the one stage test, a summation of the active clotting and anticlotting factors, gives an estimate of above 10 per cent (Figs. 2 and 3).

SUMMARY

1. Prothrombin estimation is at present a bio-assay, and to understand the various methods a knowledge of the mechanism of blood coagulation is essential. Blood clots in two stages. In the first stage, prothrombin in the presence of thromboplastin, prothrombin accelerator and calcium, is converted to thrombin. In the second stage, thrombin converts fibrinogen to fibrin. Variation in these and other factors may influence the normal physiologic clotting of blood.

2. Methods used today for measuring prothrombin are for the most part based on the so-called one stage or two stage methods. The one stage test, in that it leaves uncontrolled a number of factors other than prothrombin and in that it allows the two phases of clotting to go on concurrently, is not a measure of prothrombin but is rather a measure of the over-all clotting activity of blood under certain specific conditions. The two stage method, on the other hand, by controlling most of the coagulation and anticoagulation factors and by taking into consideration the two stages by which blood clots, is a more accurate measure of the available prothrombin.

3. It is often clinically more important to know the over-all clotting activity of the blood than to know the concentration of prothrombin. In such instances, namely certain bleeding tendencies, information given by the one stage test may be more important than that given by the two stage method. In conditions in which an accurate prothrombin estimate is important, i.e. suspected liver damage and particularly in the control of dicumarol

therapy, the two stage method is the one of choice.

4. It can hardly be overemphasized that an understanding of what each method represents is of prime importance in the selection of the particular test needed and in the interpretation of the results obtained.

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STUDIES IN EXPERIMENTAL FROSTBITE

V. Further Evaluation of Early Treatment

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RECENT experiments have indicated that, in contradistinction to some of the views formerly held, rapid thawing and the production of vasodilatation may be of value in minimizing tissue loss after frostbite; anticoagulant therapy also appears to be somewhat helpful. In contrast, the early treatment of experimental frostbite by prolonged local cooling of the frozen part results in an increased loss of tissue (13). In view of the difficulty or impossibility of controlling adequately any given method of treatment in cases of human frostbite and in view of the chance of error in transferring the results of animal experimentation to man, we have felt it advisable to extend our investigations. We have hoped that the possible clinical significance of any benefit of treatment might be increased if similar results should be found to obtain in a number of different species and in the treatment of cold injuries to parts varying widely in vascularity and in relative proportion of skin and muscle mass.

MATERIALS AND METHODS

Healthy white mice weighing from 20 to 25 grams, domestic albino rats weighing from 150 to 200 grams, white rabbits weighing from 1 to 2½ kilograms, and mongrel dogs were used. The cold injury was inflicted under anesthesia. The mice and rats were anesthetized by intraperitoneal injection of 10 cubic centimeters per kilogram of body weight of 0.6 per cent solution of nembutal sodium. The rabbits were anesthetized by the slow intravenous injection of 6 per cent nembutal sodium or 2½ per cent pentothal sodium until sleep was induced. The dogs were anesthetized with intravenously administered 6 per cent nembutal sodium, 0.43 cubic centimeter per kilogram of body weight. Ether was used to supplement the anesthesia in the few rabbits and dogs in which it was necessary.

In all experiments the part to be frozen was immersed directly in ether kept cooled to the desired temperature with solid carbon dioxide. In all instances the duration of freezing was measured from the time of actually observed solidification of the part to the time of its withdrawal from the freezing mixture. The extent of the part frozen was as follows: the distal 6 centimeters of the tail in mice, the distal 7 centimeters of the tail in rats, the distal 5 centimeters of the ears in rabbits, and the hind foot up to the hock in mice, rats, rabbits, and dogs. The area to be frozen in the tails of mice and rats and in the ears of rabbits was delineated by a line drawn across the proximal margin with indelible ink. The tails of mice and rats were frozen for 5 seconds at −15 degrees C., the feet of mice and rats for 5 seconds at −20 degrees C., the ears of rabbits at −15 degrees C. for 2 minutes, the feet of rabbits at −15 degrees C. for 5 minutes, and the feet of dogs at −25 degrees C. for 15 minutes. Both ears were frozen in each rabbit and both feet in each dog. In those experiments in which sympathectomy was performed this procedure was used to denervate only one ear or one foot, the other serving as a control. In the mice and rats only one foot was frozen. No dressing was applied to the frozen part except in the case of the feet of rabbits; these were dressed with sulfathiazole ointment and a nonconstricting sterile bandage.

The interval between freezing and thawing was noted in all instances. Periodically, notes were made concerning temperature, color, edema, vesiculation, ulceration, and gangrene. All animals subjected to freezing were observed carefully until the extent of death of tis-

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sue was established, until healing had occurred, or until it was apparent that no tissue loss was sustained.

In those animals treated by rapid thawing, the frozen part was placed in a water bath kept at the desired temperature. The period of immersion in the warm water was 2 minutes in the case of the tails of mice and rats, the feet of mice and rats, the ears of rabbits; it was 5 minutes in the case of the feet of rabbits and dogs.

In the anticoagulant experiments aqueous heparin was administered subcutaneously to rats according to the following regimen. One milligram was given initially and every 3 hours for the first 9 hours, followed by 0.5 milligram every 3 hours for the following 63 hours. Coagulation time estimations were carried out by the Kruse-Campbell method (9) in control animals treated in the same manner.

In the experiments with tetraethyl ammonium chloride the drug was administered in rats intraperitoneally in a dosage of 25 milligrams per kilogram of body weight every hour for the first 8 hours and every 4 hours for the following 64. In rabbits 20 milligrams per kilogram of body weight were given by the same route and according to the same schedule. The effect of the drug upon the skin temperature of the rat's tail and the rabbit's ear was ascertained by thermocouple observations in control animals given the drug in like fashion.

Cervical sympathectomy in rabbits was accomplished by resection of all the cervical sympathetic chain; a Horner's syndrome resulted in all instances. In dogs all or nearly all of the lumbar sympathetic chain was removed through an extraperitoneal approach. In those animals in which sympathetic denervation was carried out after freezing the exposure was made beforehand in order to facilitate extirpation of the ganglionated chain after freezing.

RESULTS

The tails and feet of mice and rats, the ears of rabbits, and the feet of dogs all froze solidly as soon as immersed in the freezing mixture. In some instances a short interval elapsed before the feet of rabbits became solidified. When solidly frozen the parts were hard, white, and opaque. During and immediately after freezing marked shivering of the animals was common. Thawing took place at a variable time following freezing with return of color, warmth, and pliability. Thawing generally proceeded from the proximal to the distal portions of the frozen parts. In a few exceptional instances a dog's foot was observed to thaw in the reverse fashion, the distal portions before the proximal.

TABLE I.—INFLUENCE OF TEMPERATURE UPON EFFECT OF RAPID THAWING OF TAILS OF MICE FROZEN AT −15 DEGREES C. FOR 5 SECONDS*

Temperature of thawing bath	No. of animals	Mean loss of tissue in cm.	Diff. / S.E. diff.	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good and excellent results	Diff. / S.E. diff.
Air thawed controls	44	4.1		4.5		9.1	
38°C	43	2.2	2.5	2.3	0.6	30.2	2.5
42°C	40	1.0	9.6	17.5	1.9	65	6.4
50°C	40	4.0	0.19	0		5	0.64

*In this and all subsequent tables the significance of the result is expressed by calculation of the quotient of the difference of the two means or proportions and the standard error of the differences of the two means or proportions. Results are considered significant when two means or proportions differ by more than twice the standard error of the differences. Values approaching 2 indicate probable significance. A value of 2½ signifies that the result would occur by chance only once in 80 times, a value of 3 only once in 370 times.

Freezing was usually followed by edema of moderate degree. The edema generally began to subside after the second day. Often vesiculation and weeping of skin could be observed. If gangrene were to develop it was usually evident within the first 48 hours, the area becoming cold, cyanotic, and avascular in appearance. As time passed typical dry, black gangrene developed in some instances.

The effect of rapidly thawing the frozen part. Since previous studies with rapid thawing had all been carried out by warming the frozen part in water maintained at about 42 degrees C. (1, 3, 6, 13), experiments were made to ascertain whether this temperature was indeed the ideal temperature to be used. The results are recorded in Table I. When the tails of mice were frozen for 5 seconds at −15 degrees C. the mean loss from gangrene was 4.1 centimeters of tail. In only 2 or 4.5 per cent was the result excellent and in only 4 or 9.1 per cent did a good or excellent result obtain. A result was considered excellent if no loss of tissue was sustained, good if less than 1 centi-

TABLE II.—RESULTS OF RAPID THAWING IN EXPERIMENTAL FROSTBITE

Species	Part frozen	Untreated Series				Treated Series						
		No. of animals	Mean loss of tissue in cm.	Per cent with excellent results	Per cent with good or excellent results	No. of animals	Mean loss of tissue in cm.	Diff. / S.E. diff.	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Mouse	Tail	44	4.1	4.5	9.1	40	1.0	9.6	17.5	1.9	65	6.4
Rat	Tail	43	3.6	8.8	13.7	47	1.3	5.3	51	5.2	72.3	6.2
Mouse	Foot	36		0	5.6	25			48	4.9	76	7.5
Rat	Foot	22		0	50	31			38.8	4.4	87.6	4.0
Rabbit	Foot	12		0	0	15			46.7	2.9	100	
Dog	Foot	20		15	20	9			11.1		66.6	2.5
Rabbit	Ear	39		0	5.1	20			75	7.8	95	14.7

meter of tissue was lost. The average time from freezing to thawing in this control group was 2.3 minutes. Forty animals similarly frozen but treated by immediate immersion of the tail in water kept at 42 degrees C. fared much better. The mean loss of tail was 1.0 centimeter, the percentage with excellent result 17.5 and with good or excellent result 65. When the temperature of the bath was kept at 38 degrees C. the results were only moderately better than in the control series. The mean loss of tissue was 2.2 centimeters, the proportion with excellent result 2.3 and with good or excellent result 30.2. When a temperature of 50 degrees C. was used the results were no better than in the control group. The mean tissue loss was 4.0 centimeters, the percentage with excellent result zero, and with good result 5. The average body temperature of mice was found to be 38.7 degrees C., in unanesthetized, and 35.8 degrees C., in anesthetized animals.

In Table II are tabulated the results of treating by rapid thawing at 42 degrees C. frostbite in the tails of mice and rats, in the feet of mice, rats, rabbits, and dogs, and in the ears of rabbits. It is evident that a striking reduction in loss of tissue resulted from rapid thawing in all instances. In the case of the tails of rats the same criteria were used for excellent and good results as in the experiments with the tails of mice. Excellent results occurred in 8.8 per cent of untreated and in 51 per cent of treated animals. Good or excellent results obtained in 13.7 per cent of untreated and in 72.3 per cent of treated animals. The mean loss of tissue was 3.6 centimeters in the first and only 1.3 centimeters in the second group. In experiments in which the feet of mice, rats, rabbits, and dogs were frozen, the result was classified as excellent if no loss of tissue other than nails was sustained. The result was considered good if the loss of tissue was limited to toes. In mice treatment increased the excellent outcome from zero to 48 per cent and the good and excellent results from 5.6 to 76 per cent. In rats the excellent results were increased from zero to 38.8 and the good and excellent results from 31.2 to 80.7 per cent. In rabbits no untreated animal had either a good or excellent result, while in the treated group 46.7 had an excellent and the remainder a good result. In dogs the proportion with no loss of tissue was not increased by treatment but the proportion with a good or excellent result was increased significantly from 20 to 66.6 per cent. In the experiments with frostbite of the ears of rabbits the outcome was judged excellent if no tissue loss was sustained; it was judged good if only partial loss of the frozen area was sustained. In the control group there were no excellent and few (5.1 per cent) good results while in the treated group 75 per cent had excellent and 95 per cent good or excellent results.

In Table III are recorded data comparing the results of immediate warming of the frozen tails of mice and rats with the control air-thawed group and with other animals in which, after thawing, the part was immersed for the same interval (2 minutes) in a water bath kept at the same temperature (42°C.) as in the first group. It is apparent that warming the

TABLE III.—COMPARISON OF EFFECT OF RAPID THAWING AND OF LOCAL WARMING OF PART AFTER SPONTANEOUS THAWING. STUDIES WITH MICE AND RAT TAILS FROZEN FOR 5 SECONDS AT —15 DEGREES C.

Species	Treatment	No. of animals	Mean loss of tissue in cm.	Diff. / S.E. diff.	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Mouse	None	44	4.1		4.5		9.1	
	Rapid thawing at 42°C	40	1.0	9.6	17.5	1.9	65	6.4
	Air thawing, then warming at 42°C.	20	4.25	0.44	0		0	
Rat	None	43	3.6		8.8		13.7	
	Rapid thawing at 42°C	47	1.3	5.3	5	5.2	72.3	6.2
	Air thawing, then warming at 42°C	20	4.4	0.4	5.0	0.6	20	0.5

TABLE IV.—EFFECT OF HEPARINIZATION IN THE PREVENTION OF GANGRENE AFTER FREEZING THE TAILS OF RATS FOR 5 SECONDS AT —15 DEGREES C. AND THE FEET OF RATS FOR 5 SECONDS AT —20 DEGREES C.

Part frozen	Treatment	No. of animals	Mean loss of tissue in cm.	Diff. / S.E. diff.	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Tail	None	43	3.6		8.8		13.7	
	Immediate heparinization	39	2.2	2.9	17.9	1.2	28.1	1.6
	Heparinization begun 3 hours after freezing	46	3.8		13.0	0.6	19.5	0.73
Foot	None	22			0		50	
	Immediate heparinization	38			18.4	2.9	57.9	0.6
	Heparinization begun 3 hours after freezing	41			4.9	1.5	68.3	1.4

frozen part after thawing had occurred did not appreciably affect the result of freezing, the outcome being quite like that in the untreated control group.

The effect of anticoagulant therapy. Studies in control animals revealed that the regimen of heparinization in rats previously outlined was effective in maintaining a satisfactory prolongation of coagulation time. Larger doses of heparin were found to be attended with a prohibitively high mortality. The coagulation time of normal rats varied from 1 to 3 minutes, averaging 1.5. With the routine of heparinization used, the coagulation time ranged from 4 to 5 minutes, averaging 4.5; it was longer during the first 9 hours when 1 milligram rather than 0.5 was given each 3 hours. The results of treatment are recorded in Table IV. With immediate heparinization the results with frozen tails were significant as judged by mean loss of tissue, but, though suggestively so, were not definitely significant as judged by the proportion of good and excellent results. When anticoagulant treatment was delayed until 3 hours after freezing, the results were not significant. In rats with frozen feet immediate heparinization brought about a significant increase in the proportion of excellent results. No definite effectiveness could be demonstrated as judged by the proportion of good results. With delayed heparinization the good and excellent results, though slightly better than in the control series, were not significant. When rapid thawing and heparinization were combined, the results were not appreciably improved in preventing gangrene in frostbite of the rat's foot and were slightly less good in frostbite of the rat's tail as compared with the results of rapid thawing alone (Table V).

The effect of tetraethyl ammonium chloride. In Table VI are recorded the results of treating frostbite in the tails and feet of rats and in

TABLE V.—EFFECT OF RAPID THAWING AND HEPARINIZATION IN PREVENTION OF GANGRENE AFTER FREEZING THE TAILS OF RATS FOR 5 SECONDS AT —15 DEGREES C. AND THE FEET OF RATS FOR 5 SECONDS AT —20 DEGREES C.

Part frozen	Treatment	No. of animals	Mean loss of tissue in cm.	Diff. / S.E. diff.	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Tail	None	43	3.6		8.8		13.7	
	Rapid thawing	47	1.3	5.3	51	5.2	72.3	6.2
	Rapid thawing and immediate heparinization	42	1.7	5.4	33.3	2.9	55.4	4.3
Foot	None	22					50	
	Rapid thawing	31			38.7	4.4	87.6	4.0
	Rapid thawing and immediate heparinization	34			41.2	4.9	96.7	4.2

TABLE VI.—EFFECT OF TETRAETHYL AMMONIUM CHLORIDE IN THE PREVENTION OF GANGRENE AFTER FREEZING THE TAILS OF RATS AT —15 DEGREES C. FOR 5 SECONDS, THE FEET OF RATS AT 20 DEGREES C. FOR 5 SECONDS, AND THE EARS OF RABBITS AT —15 DEGREES C. FOR 2 MINUTES

Species	Part frozen	Treatment	No. of animals	Mean loss of tissue in cm.	Diff. / S.E. diff.	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Rat	Tail	None	43	3.6		8.8		13.7	
		TEAC Immediate	41	2.5	2.5	12.1	0.5	37.9	2.6
		TEAC 1 hour after freezing	41	1.4	6.8	37.9	3.3	62.3	5.3
Rat	Feet	None	22			0		50	
		TEAC immediate	47			10.6	2.6	93.5	3.9
		TEAC 1 hour after freezing	43			9.3	2.2	72.1	1.8
Rabbit	Ears	None	39			0		5.1	
		TEAC immediate	8			0		0	

the ears of rabbits with tetraethyl ammonium chloride. The dosage used was found to cause a variable rise in skin temperature of the tails of normal rats, the temperature tending to fall to normal toward the end of an hour; the average increase in temperature noted in these control observations was 1.5 degrees C. It should be noted that the tails of normal rats seemed to be in a state of near maximal vasodilatation in the environment of the laboratory. Larger doses of tetraethyl ammonium chloride were unsatisfactory because of fatalities associated with their use. When treatment was instituted immediately after freezing the results were significant from the standpoint of mean loss of tissue and the good results obtained, though no increase in the proportion of animals with no loss of tissue was observed. When treatment was delayed for 1 hour the results were, peculiarly enough, even better, 37.9 per cent having an excellent result as compared with 8.8 in the untreated group, 62.3 per cent having a good or excellent result as compared with 13.7, and the mean loss of tail being only 1.9 centimeters as compared with 3.6 centimeters. In the experiments with frozen feet, immediate treatment increased the proportion of excellent results from zero to 10.6 and of good and excellent results from 50 to 93.5. The results were not quite as good when treatment was delayed for 1 hour. The rabbits treated with tetraethyl ammonium chloride fared no better than the untreated animals.

In Table VII are compared the results with tetraethyl ammonium chloride in combination

TABLE VII.—EFFECT OF RAPID THAWING AND TETRAETHYL AMMONIUM CHLORIDE IN PREVENTION OF GANGRENE AFTER FREEZING THE TAILS OF RATS AT —15 DEGREES C. FOR 5 SECONDS AND THE FEET OF RATS AT —20 DEGREES C. FOR 5 SECONDS

Part frozen	Treatment	No. of animals	Mean loss of tissue in cm.	Diff. / S.E. diff.	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Tail	None	43	3.6		8.8		13.7	
	Rapid thawing	47	1.3	5.3	51	5.2	72.3	6.2
	Rapid thawing and immediate TEAC	48	1.7	6.3	35	3.2	62.5	5.5
Feet	None	22			0		30	
	Rapid thawing	31			38.7	4.4	87.6	4.0
	Rapid thawing and immediate TEAC	50			40	7.1	100	4.7

TABLE VIII.—EFFECT OF SYMPATHECTOMY IN PREVENTION OF GANGRENE AFTER FREEZING THE EARS OF RABBITS AT —15 DEGREES C. FOR 2 MINUTES AND THE FEET OF DOGS AT —25 DEGREES C. FOR 15 MINUTES.

Species	Treatment	No. of animals	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Rabbit	None	39	0		5.1	
	Sympathectomy performed 10 days before freezing	15	0		0	
	Sympathectomy immediately after freezing	10	0		0	
Dog	None	20	15		20	
	Sympathectomy immediately after freezing	20	35	1.5	45	1.7

with rapid thawing, rapid thawing alone, and no treatment. The use of tetraethyl ammonium chloride appears to have added no protection over that afforded by rapid thawing alone.

The effect of sympathectomy. From Table VIII it is apparent that sympathetic denervation was of no benefit in preventing gangrene in the frostbitten ears of rabbits. All of the ears treated by sympathectomy either before or after freezing developed complete gangrene. It is of some interest, however, that the onset of gangrene appeared to have been delayed for about 24 hours in all except 2 of the ears, as compared with the untreated controls. No difference was noted in the thawing time of treated and untreated ears.

It appears, however, that sympathectomy may have been of benefit in treating the frozen feet of dogs. Thirty-five per cent of the feet treated by sympathectomy sustained no loss of tissue as compared with 15 per cent in the untreated group. There was a good or excellent result in 45 per cent of the treated as compared with 20 per cent in the untreated group. These results are of probable significance. It should be pointed out that in all the experiments we are reporting there was a remarkable uniformity with regard to the time between frostbite and thawing except in the case of the feet of dogs. Here there were wide differences noted from animal to animal. The thawing time varied from 12 to 72 minutes. In 18 of the 20 dogs the sympathectomized and control feet thawed in the same, or approximately the same time. In one instance the denervated foot thawed in 19 minutes while the contra-

TABLE IX.—EFFECT OF SYMPATHECTOMY IN PREVENTION OF GANGRENE AFTER FREEZING THE FEET OF DOGS AT —25 DEGREES C. FOR 15 MINUTES

No. of animals	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
17	0		5.9	
17	23	2.2	35.3	2.3

TABLE X.—EFFECT OF SYMPATHECTOMY COMBINED WITH RAPID THAWING IN PREVENTION OF GANGRENE AFTER FREEZING THE EARS OF RABBITS AT —15 DEGREES C. FOR 2 MINUTES AND THE FEET OF DOGS AT —25 DEGREES C. FOR 15 MINUTES.

Species	Treatment	No. of animals	Per cent with excellent results	Diff. / S.E. diff.	Per cent with good or excellent results	Diff. / S.E. diff.
Rabbit	None	39	0		5.1	
	Rapid thawing	20	75	7.8	95	14.7
	Rapid thawing and sympathectomy performed after freezing	6	50	2.4	83.3	5.
Dog	None	20	15		20	
	Rapid thawing	9	11.1		66.6	2.5
	Rapid thawing and sympathectomy performed after freezing	9	55.5	2.6	76.6	2.8

lateral foot was not thawed completely for 65 minutes; the treated foot survived without gangrene while gangrene was complete in the other. In a second animal there was a marked difference in thawing time in the opposite direction. The treated foot thawed more slowly and in this case, though gangrene was extensive in both feet, it was less massive in the untreated control foot. It is perhaps of some significance that in 3 animals the thawing time was short and gangrene did not develop in either foot. If these 3 animals are not considered and the results in the remaining 17 are analyzed (Table IX) the benefit of sympathetic denervation appears to be more significant, the excellent results in the two groups being zero and 23 per cent, the good and excellent results 5.9 and 35.3.

When sympathectomy was used in conjunction with rapid thawing (Table X) the results with the frozen ears of rabbits were no better than those obtained with rapid thawing alone. The proportion of excellent results obtained in the treatment of the frozen feet of dogs, however, appears to have been significantly increased as compared with the results obtained with rapid thawing alone.

The edema present during the first few days after freezing was somewhat greater in the ears of rabbits which had been sympathectomized either before or after freezing as compared with the untreated ears. There also appeared to be more edema for the first 2 days in the sympathetically denervated feet of dogs than in the untreated controls' feet. After the first 48 hours the edema appeared to be about equal and to subside at an equal rate. In 5 of those animals treated by rapid thawing, however, the edema was distinctly less in the sympathectomized foot; in the other 4 the edema was roughly the same in the two feet.

In the environment of the laboratory the ears of rabbits subjected before freezing to sympathetic denervation were on the average 1 degree warmer than the contralateral normally innervated ears. Wide fluctuations were observed after freezing from about 6 minutes after thawing, until beginning gangrene was apparent. Most of the denervated ears were warmer than the others, the difference in temperature being as great as 5 degrees C. and averaging about 1 degree. The sympathetically denervated feet of dogs also were warmer after freezing than the contralateral normally innervated feet. When both feet were rapidly thawed the temperature of the two feet was roughly the same in 3 while in 6 dogs the sympathectomized foot was warmer.

DISCUSSION

The studies reported demonstrate a remarkable efficacy of immediate rapid thawing of the frozen part in preventing loss of tissue. It is furthermore of considerable interest that in our experiments when the frozen part was preserved by such treatment, the part was normal in appearance and seemed to have normal sensation and motor function. In the experiments of Harkins and Harmon comparing rapid and slow thawing of frozen legs of dogs and ears of rabbits no conclusion could be reached other than that rapid thawing did not increase tissue damage. Using the ears and feet of rabbits Ariev found rapid thawing to be very effective.

The same was true in the experiments of Fuhrman and Crismon (4) in which the ears and feet of rabbits were frozen. It was also the case in the experiments of Lempke and Shumacker (13) with the frozen tails of mice. It would seem clear that the evidence for the therapeutic efficacy of immediate rapid thawing is now well established from studies in several species and in treating frostbite in parts varying widely in vascularity and tissue structure.

Our studies revealed that the use of tetraethyl ammonium chloride was effective in treating the frozen tails and feet of the rat but no efficacy was demonstrated in treating the frozen ears of rabbits. No significant improvement over the results obtained with rapid thawing alone was noted when the tails and feet of rats were treated by rapid thawing and tetraethyl ammonium chloride. Lempke and Shumacker (13) had found tetraethyl ammonium chloride probably significantly effective in preventing loss of tissue in the frozen tails of mice and this drug combined with rapid thawing appeared to be better than either therapeutic agent alone. Fuhrman and Crismon (5) had reported that carbon dioxide, nitroglycerine, and acetyl B methyl choline were ineffective in preventing gangrene following frostbite of the ears and feet of rabbits.

We did not find that sympathectomy performed either before or immediately after freezing was helpful in preventing gangrene in the rabbit's ear. Sympathectomy performed immediately after freezing seemed probably significantly effective in preventing tissue damage in the feet of dogs. Years ago Lake had found less vesiculation and necrosis in human subjects, who had volunteered for freezing experiments, when the area of skin to be frozen was denervated by a field block. Crismon and Fuhrman (2) reported that anesthetization of the stellate ganglion delayed the onset of vascular stasis in the frozen ears of rabbits though it had no effect upon the final outcome except to delay for 1 day the appearance of gangrene. With mild freezing of rabbit ears no essential difference in tissue damage was evident in Kreyberg's (7, 8) experiments in which one ear had been sympathetically denervated the day before freezing. Previous sympathectomy did not adversely influence the end result in frostbite of the dog's foot in the experiments of Lempke and Shumacker (14); the denervated foot, if anything, did a trifle better than the controls. Altogether the evidence would suggest that the production of vasodilatation has never proved harmful in experimental frostbite and, though variable results have been obtained, has tended to be beneficial.

Our studies with immediate heparinization of rats gave suggestive evidence of some efficacy in limiting the damage from frostbite of the tail and foot. Judged by mean loss of tissue the results were significant in experiments with freezing the tail. The proportion of good and excellent results was not definitely significantly increased. Heparinization increased significantly the proportion of feet surviving without any loss of tissue but did not increase the proportion with gangrene limited to the toes. When heparinization was deferred until 3 hours after freezing the results were no better than in untreated animals. Heparinization combined with rapid thawing did not improve the results over those observed with rapid thawing alone. Apparently no one has succeeded in obtaining the brilliant results Lange and his associates (3, 11, 12) originally reported in studies with frostbite of the rabbit's foot. Fuhrman and Crismon (5) did not find heparin effective in diminishing gangrene in the frozen feet of rabbits nor did Quintanilla, Krusen, and Essex find heparin of value in their studies with the frostbitten rabbit's ear. Shumacker and his associates did find that heparin had some limited efficacy in treating frostbite of the rabbit's foot and Lempke and Shumacker (13) found heparin of value in treating frostbite of the mouse's tail. In these last experiments, and in our own present study, heparinization was less effective than rapid thawing. In mice it was a somewhat better therapeutic agent than tetraethyl ammonium chloride and, in rats, somewhat less effectual.

With the extensive experimental data now available it would appear reasonable cautiously to apply these therapeutic aids in treating human frostbite. It might be anticipated that rapid thawing of the frozen part at a temperature just above body temperature would prove of great value. It would seem justifiable to

use, in addition, sympathetic blocks, autonomic blocking agents, or sympathectomy. The use of anticoagulants should also be given clinical trial.

CONCLUSIONS

Experiments are reported which demonstrate remarkable efficacy of rapid thawing in the early treatment of experimental frostbite in the tails, feet, and ears of a number of species. The production of vasodilatation by use of tetraethyl ammonium chloride and sympathetic denervation gave more variable results but in general seemed beneficial. Immediate heparinization was of some value.

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A FURTHER REPORT ON DICUMAROL PROPHYLAXIS AGAINST VENOUS THROMBOSIS IN WOMEN UNDERGOING SURGERY

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BY way of introduction it is interesting to note that thrombosis is a normal phenomenon only in relation to reproductive processes in women. The only apparently physiological thrombosis in human beings is that which follows ovulation, accompanies the endometrial degeneration of menstruation, takes place in some of the decidual vessels during pregnancy and occurs with the placental-decidual degeneration of parturiency. Parenthetically, whether these processes are truly normal is subject to philosophical deliberation based on comparative phylogeny, some laboratory findings, and ordinary observation. All other thrombosis is frankly pathological or physiological in a restricted sense in that it is a part of the healing response to pathological conditions involving injury of blood vessels.

There are three main angles to the problem of pathological thrombosis: vascular injury, stasis of blood, and the coagulability of blood. From the surgical aspect the reduction of vascular injury in the operative area is a matter of technical refinement. Whether vascular injury occurs in the legs during and after operation is unknown. More likely the varicose veins so often present are evidence of already existing damage and the stasis of blood and perhaps an increase of its coagulability, brought about by surgery or the disease requiring surgery or just the condition of the patient, favor the development of thrombosis. As regards the second angle, without the enumeration of details, the statement appears valid that all the improvements in the care of patients before, during, and after operation in the last 2 decades have as their main object or one of their objects the prevention of stasis of blood in the legs and pelvis. The third angle has been approached through investigations concerning blood coagulation and the use of heparin and dicumarol as adjuvants in the prevention and treatment of pathological thrombosis occurring in relation to surgery. I apply the term "adjuvant" to these anticoagulants advisedly because experience has taught that they cannot be relied upon to the complete exclusion of venous interruption for avoiding embolism.

The following is an interval report concerning a clinical experiment which is still in progress. Its purpose was and is to determine whether dicumarol, given in conservative doses so as to avoid hemorrhage as well as the necessity of extensive laboratory control, would have any demonstrable effect in reducing postoperative thromboembolic crises. It was realized that such use of dicumarol could at best be but a contributory factor in a program of prevention which included all the accepted measures for averting these crises.

The majority of the women selected for treatment were ward patients over 35 years of age undergoing major and vaginal plastic surgery, the major surgery being for the most part pelvic. This is the group in which the highest incidence of thrombosis and fatal embolism is known to occur. Administration of the drug was begun on January 31, 1943; a superficial examination of results was made for the 4 year period ending January 31, 1947, and published (1); the present critical evaluation covers the 6 year 5 month interval ending June 30, 1949.

Administration of dicumarol. During the first few months of this investigation dicumarol was given preoperatively in 200, 300, and occasionally 400 milligram amounts. Between May, 1943, and February, 1947, most patients

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TABLE I.—INCIDENCES OF POSTOPERATIVE THROMBOEMBOLIC COMPLICATIONS BEFORE AND DURING THE PERIOD OF TREATMENT WITH DICUMAROL

	Thrombosis		Nonfatal embolism		Fatal embolism	
	No. of cases*	Incidence	No. of cases	Incidence	No. of cases	Incidence
Before dicumarol						
1922 to Jan. 30, 1943, incl. 31,950 patients	355	1 : 90	74	1 : 432	66	1 : 484
1940 to Jan. 30, 1943, incl. 6,833 patients	89	1 : 76	14	1 : 488	9	1 : 759
During dicumarol						
Jan. 31, 1943 to June 30, 1949, 15,043 patients	62	1 : 257	19	1 : 839	6	1:2657

*In this and the following tables the number of cases of thrombosis includes those of embolism.

TABLE II.—INCIDENCES OF POSTOPERATIVE THROMBOEMBOLIC COMPLICATIONS IN SIMILAR GROUPS, VIZ., WARD PATIENTS OVER 35 YEARS OF AGE WHO HAD MAJOR AND VAGINAL PLASTIC SURGERY, BEFORE AND DURING TREATMENT WITH DICUMAROL

	Thrombosis		Nonfatal embolism		Fatal embolism	
	No. of cases	Incidence	No. of cases	Incidence	No. of cases	Incidence
1940 to Jan. 30, 1943, incl. 2,272 patients	53	1 : 43	8	1 : 284	6	1 : 379
Jan. 31, 1943 to June 30, 1949, incl. 849 patients —no dicumarol	11	1 : 77	1	1 : 849	2	1 : 424
Jan. 31, 1943 to June 30, 1949, incl. 3,078 patients received dicumarol	25	1 : 123	7	1 : 440	3	1:1026

received the drug 1 to 2 days postoperatively and again 5 days later. A third dose was prescribed after an additional 5 days if the patient was still in bed. The first 2 doses consisted of 200 milligrams for patients weighing more than 60 kilograms and 100 milligrams for those weighing less. The third dose was 100 milligrams. Starting in the fall of 1946 and with increasing frequency, administration was begun the night before operation, the second dose being given 4 to 5 days later. Since January, 1947, this has been the routine procedure. Fifty per cent of all the patients treated from January, 1943, through June, 1949, received the drug in this manner. Third doses have only occasionally been prescribed, because most patients have been up and about before the eighth postoperative day and because it seemed desirable to find out whether there might be less chance for thrombosis after they had had dicumarol in this fashion and had become ambulatory. Hemorrhagic complications have been few, transitory, and only temporarily disturbing. There have been no deaths from dicumarol. In 1 instance already reported (1) it might have been a contributory cause of death. This was a case of subarachnoid hemorrhage.

Laboratory procedure. Frequent determinations of prothrombin time were performed during the early months of this experiment in order to gain information concerning the amount, duration, and variation of the effect of dicumarol. Sufficient determinations were run to show that the amounts prescribed cause the prothrombin time to be appreciably prolonged in most women by the second day after ingestion, this effect usually lasting 2 to 5 days and occasionally longer. By the fall of 1944 it became customary to have this test done but once in most patients, on the fourth or fifth day after the first dose, so as to discover any really overresponsive individuals. In recent months these routine determinations have been omitted as unnecessary.

Comparative figures and comments. In Table I the overall incidence of postoperative thromboembolic complications in all patients operated upon, both ward and private, before and during the dicumarol study, are compared. The figures for 1940 through January 30, 1943, are given separately to demonstrate that even during the years just preceding this study there was no impressive change from previous years. Although these comparisons show a gratifying change since January, 1943, they are too general to give a clue concerning any role of dicumarol in it. Therefore, in Table II the incidences of thromboembolic complications in similar groups of patients are compared. The women comprising these groups were ward patients over 35 years of age. Sixty per cent of them had had major surgery and the remainder vaginal plastic operations. Hysterectomies numbered 2,604, 70 per cent of the major operations. Except in the matter of nonfatal embolism, the figures for the dicumarol group suggest some improvement. The

TABLE III.—INCIDENCES OF THROMBOEMBOLIC COMPLICATIONS BEFORE THE FIFTEENTH POSTOPERATIVE DAY (SAME GROUPS OF PATIENTS AS IN TABLE II)

	Thrombosis		Nonfatal embolism		Fatal embolism	
	No. of cases	Incidence	No. of cases	Incidence	No. of cases	Incidence
1940 to Jan. 30, 1943, incl. 2,260 patients	41	1 : 55	7	1 : 377	3	1 : 753
Jan. 31, 1943 to June 30, 1949, incl. 846 patients —no dicumarol	8	1 : 106	1	1 : 846	2	1 : 423
Jan. 31, 1943 to June 30, 1949, incl. 3,072 patients received dicumarol	19	1 : 162	5	1 : 614	1	1:3072

TABLE IV.—THROMBOEMBOLIC COMPLICATIONS AMONG PRIVATE PATIENTS COMPARED WITH THOSE AMONG WARD PATIENTS TREATED WITH DICUMAROL

	Thrombosis		Nonfatal embolism		Fatal embolism	
	No. of cases	Incidence	No. of cases	Incidence	No. of cases	Incidence
1. 1940 to Jan. 30, 1943, incl. 600 private patients	14	1 :43	2	1 : 300	2	1 : 300
2. Jan. 31, 1943 to June 30, 1949, incl. 2,068 private patients—no dicumarol	14	1 : 148	9	1 : 230	1	1:2068
3. Jan. 31, 1943 to June 30, 1949, incl. 3,078 ward patients receiving dicumarol	25	1 : 123	7	1 : 440	3	1:1026
1′. Same group as above, omitting those whose thrombosis was diagnosed after the fourteenth postoperative day	13	1 : 46	2	1 : 300	0	0 : 599
2′. Same group as above	13	1 : 159	8	1 : 259	1	1:2067
3′. Same group as above	19	1 : 162	5	1 : 614	1	1:3072

decrease in fatal embolism might have been due to the fact that vein interruption was immediately performed in 6 of the 7 women with nonfatal embolism. Emergency anticoagulant therapy was given to 4 of these and to the 1 patient whose veins were not divided. According to a statistical evaluation made by Dr. Olive W. Smith, however, the figures in Table II give no evidence of improvement that may be attributed solely to dicumarol.

Only a small number of women received dicumarol after the seventh postoperative day. Therefore, in most patients any anticoagulant effect of the drug must have vanished by the fourteenth postoperative day. Six of the dicumarol-treated group had thrombotic complications after this time, 2 patients getting nonfatal embolism on the fifteenth and seventeenth days, respectively, and 2 dying of embolism on the twenty-third and twenty-sixth days, respectively. Only in the past year, June, 1948, to June, 1949, have these late episodes occurred. Because of this experience, 100 milligram amounts of dicumarol are now being administered every 4 or 5 days, after the second dose of 100 or 200 milligrams, for as long as the patients of this group remain in the hospital. In Table III the same series of cases as in Table II are compared after omitting those cases of thrombosis following the fourteenth postoperative day. Here the figures are more indicative of value in the conservative, prophylactic use of dicumarol during the period of its administration. According to statistical analysis, the improvement in the incidences of thrombosis and fatal embolism in the treated patients is sufficiently significant to demonstrate that the drug as given was of help.

The next comparison was made between the dicumarol-treated ward patients and similar groups of private patients who did not receive any prophylactic therapy with the drug. The private patients were all over 35 years of age and had had major or vaginal plastic surgery. In all important details their care was no better than that given ward patients. As shown in the upper half of Table IV there was considerable improvement among them after January, 1943, except in the incidence of nonfatal embolism, and in this category they fared worse than the treated ward patients. Again division of veins and the emergency employment of heparin and dicumarol may have averted deaths. When the impression is taken into consideration that private patients are healthier than ward, especially after 50 years of age, the figures for the treated series do not compare too unfavorably, and certainly compare better than the control series of ward patients listed in Table II.

In the lower half of Table IV the same groups of cases as in the upper half are listed with the omission of all cases of thrombosis

which were diagnosed after the fourteenth postoperative day. Again the figures are indicative of value in the conservative use of dicumarol during the period of its action. The most significant statistical finding is that the decreased incidence of nonfatal embolism before the fifteenth postoperative day in the treated group could not have occurred by chance.

SUMMARY AND CONCLUSION

In this experiment dicumarol was given to 3,078 ward patients over 35 years of age undergoing major and vaginal plastic surgery. Fifty per cent received the drug on the first or second postoperative day and again 5 days later; 50 per cent received it the night before operation and most of these received it again 4 or 5 days later. Each dose was 200 milligrams for women weighing more than 60 kilograms and 100 milligrams for those weighing less. With a few exceptions which were not serious, this dosage required no control by prothrombin time determinations. Hemorrhagic complications were few and minor; no death was due to the drug.

Comparisons between the dicumarol-treated group and similar untreated groups, both ward and private and both before and during the time when dicumarol was used prophylactically, give fair but not striking evidence supported by statistical analysis that the drug reduced thromboembolic complications but only during the period of its action. According to this experience, its conservative use as described is a simple, safe, additional measure for helping to reduce pathological postoperative thrombosis in women undergoing abdominal and pelvic surgery without the need of extensive laboratory control.

REFERENCE

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CESAREAN SECTION AT THE CHICAGO LYING-IN HOSPITAL—1931 TO 1949

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IN 1944, in a review of the mortality rate following cesarean section the senior author compiled statistics on 6,335 cases of cesarean section from five maternity hospitals in the United States, with an uncorrected average maternal mortality rate of 1.46 per cent which ranged from 0.61 to 3.1 per cent. He stated that on any hospital service the mortality from cesarean section can be kept below 1 per cent by proper evaluation of the individual case. A similar study of cesarean sections performed since 1941 in the same hospitals indicates that in 4,497 operations, the average maternal mortality had decreased to 0.24 per cent with a range of from 0.1 to 0.58 per cent. D'Esopo, in a recent report, states that the mortality rate following cesarean section should not exceed 0.1 per cent. It is obvious that there has been a marked decrease in the maternal mortality from cesarean section during the past decade and that the senior author was too pessimistic in 1944. Let us hope that these excellent results continue.

MATERNAL MORTALITY

From May, 1931 to June 30, 1949, at the Chicago Lying-in Hospital 2,871 cesarean sections were performed with an uncorrected maternal mortality of 12 (0.42 per cent). Fifteen hundred operations with 10 maternal deaths were performed from 1931 to 1942. From March 6, 1942 to June 30, 1949, there were 1,371 consecutive cesarean sections with a death in April, 1942, from pulmonary embolism on the twenth-ninth postpartum day, and a second death in August, 1948, also from pulmonary embolism on the eight postpartum day, of a patient who had been ambulatory for the preceding week. Both operations had been performed because of severe toxemia and uneffaced cervices. Thus, during 6¼ years, over 1,100 consecutive sections had been performed with no deaths. The 12 deaths which occurred in 2,871 operations were due to: puerperal infection in 3 cases, intra-abdominal hemorrhage in 1 case, placenta previa in 1 case, cardiac disease in 1 case, eclampsia (cerebral hemorrhage) in 1 case, pulmonary embolism in 3 cases, (2 cesarean sections had been done for toxemia and 1 for placenta previa), and tuberculous meningitis in 2 cases. During the period from 1932 to 1948, 1,702 cesarean sections were performed at the New York Hospital with 15 deaths due to: infection in 6 cases, postpartum hemorrhage in 3 cases, heart disease in 1 case, embolism in 1 case, malignancy in 2 cases, and miscellaneous causes in 2 cases. The last death there from infection was in 1939. At the Philadelphia Lying-in Hospital where 1,599 cesarean sections had been performed since 1941, no deaths from infection had occurred. At Sloane's Hospital in 1,266 cesarean operations 1 death had occurred and the last death there from infection was in 1941. Obviously death from infection, the principle cause of mortality following cesarean section up to 1940, must now be considered the result of an error in judgment or of faulty operating room technique.

On our service the last death from sepsis, excluding the deaths from embolism, occurred in 1937. The low mortality rate on our service has not resulted from the use of the sulfonamide and antibiotic drugs. They are used but only as an aid to the time-proved measures of proper uterine drainage, uterine tone, blood transfusions, parenteral fluids, and the elimination of "meddlesome" obstetrics. In borderline cases, we insist that the obstetrician decide by the end of 24 hours whether the patient must be delivered by laparotrachelotomy or by vaginal route, or, if the patient shows evidence of uterine infection and the baby is undamaged, by cesarean hysterectomy, in which case most if not all of the uterus is removed. Unquestionably, we occasionally perform an unnecessary

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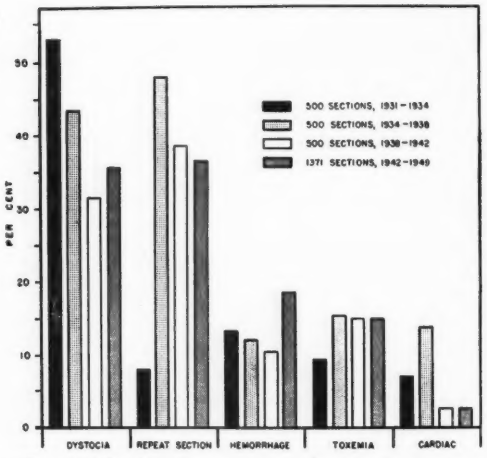

Fig. 1. Indications for cesarean section in four consecutive series. Percentage is given for each separate series.

section in which case had the patient been permitted to labor longer, conceivably she might have been delivered vaginally. We are also cognizant of the fact, since we believe "once a section, always a section," that when we have performed an unnecessary operation, we have subjected that patient to a repetition of a major operative procedure which entails a higher mortality than vaginal delivery, assuming that conditions are normal. However, in our experience the incidence of cesarean section over the past 18 years has remained constant.

Pertinent data are given in Table I A. The marked and persistent decrease in the maternal mortality is noteworthy. There has been a steady increase in the use of cesarean hysterectomy. We believe that if the patient is past 35, and ligation of the tubes is to be done, the simplest and safest operation is a hysterectomy. Furthermore, if a total hysterectomy is performed, there is no chance for cancer of the cervix or uterus to develop. This does not mean that we advocate routine total hysterectomy after the woman has had her family. However, we have ligated the tubes of patients, and in subsequent years had to treat some of these patients for menopausal and postmenopausal bleeding as well as for carcinoma of the uterus. We are now determining how frequent these complications have been.

TABLE I. —CESAREAN SECTION STATISTICS

	May, 1931 to Sept., 1934	1934 to Mar., 1938	1938 to Mar. 6, 1942	1942 to June 30, 1949	1931 to 1949
A. Incidence and maternal mortality					
Deliveries, No.	8,871	9,138	11,281	27,360	56,650
Cesarean sections, No.	500	500	500	1,371	2,871
Incidence, per cent	5.6	5.5	4.4	5.0	5.1
Low cervical, per cent	92.	93.	91.	89.	91.
Mortality, No., per cent	5 1.0	2 0.4	2 0.4	2 0.15	11 0.38
Cesarean-hysterectomy, No., per cent	30 6.0	29 5.8	37 7.4	147 10.7	243 8.5
Mortality No., per cent	0	1 3.6	0	0	1 0.41
B. Anesthesia per cent					
				1942–1948	1948–1949
Local, No.	65	57	58	37	4
Inhalation, No.	16	20	15	11	7
Local and inhalation, No.	20	25	26	18	3
Caudal and spinal, No.	0	0	0	34	82
Spinal and inhalation, No.	0	0	0	0	3

INDICATIONS FOR CESAREAN SECTION

Laparotrachelotomy and cesarean hysterectomy are the two chief types of abdominal delivery practiced on our service. There have been approximately 15 to 20 extraperitoneal cesarean sections and a few classic operations. The uterine incision in laparotrachelotomy frequently extends from 1 to 3 centimeters into the contractile portion of the uterus, but, as Dieckmann described in a previous report, the incision can be covered with bladder peritoneum, if the latter is separated as described by him. In questionable cases, a secondary Lembert or Cushing stitch is used on the bladder peritoneum.

Obstetricians are indebted to the staff of the Margaret Hague Hospital for their popularization of the extraperitoneal cesarean section and their accumulation of 1,068 operations with a maternal mortality of 0.56 per cent (6 patients) from 1931 to June 4, 1949. From 1943 to June 4, 1949, 637 such operations have been performed at that hospital with 1 death from sepsis. Of the 6 deaths, 4 were from sepsis, 1 from hemorrhage, and 1 from the spinal anesthetic.

The senior author in a recent article has reported our beliefs and practices concerning the proper use of cesarean hysterectomy. In that report the conclusion is that cesarean hysterectomy in patients with infection or potential infection ensures the lowest mortality provided that either all of the cervix is removed or at the most, only 1 to 2 centimeters are left. A peritonitis routine is necessary for 48 to 96 hours depending on the postoperative course. During this period, adequate supportive treatment is necessary and sufficient parenteral fluid must be given to ensure a urinary output of at least 1,000 milliliters per 24 hours. The mortality rate from this operative procedure should be less than 2 per cent in patients in whom infection is present. As an elective procedure, the mortality should be less than 1 per cent.

The indications for the cesarean section in the four groups are given in Figure 1. The most striking change is that due to the increase in the repeat cesarean section after the first 500. This was first pointed out by Smith, reporting from the Boston Lying-in in 1933. The percentage of repeat cesarean sections soon exceeded the number for dystocia. If the mortality rate for cesarean section is kept under a half per cent and if the incidence of cesarean section is not over 5 per cent, we see no contraindications to such a condition of affairs. In the last series there has been a definite increase in the use of cesarean section in the treatment of placenta previa. We believe very definitely that if the hemorrhage in placenta previa cannot be controlled completely by rupture of the membranes, and possibly traction with a Willett forceps, cesarean section is indicated, primarily in the interest of the mother and secondarily, in the interest of the baby. The rate of cesarean section in toxemia remains constant.

There has been a marked reduction in the use of cesarean section in cardiac patients, primarily because we no longer perform cesarean section for purposes of tubal ligation. Cesarean section in cardiac patients is only to be used when vaginal delivery is difficult or in the case of those few cardiac patients who have regained compensation and the optimum time for delivery is selected.

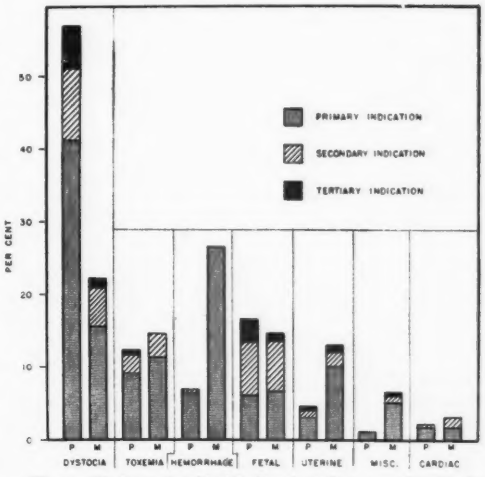

Fig. 2. Various classified indications for operation in the 1,371 cases of the last series (1942 to 1949).

In Figure 2 we have depicted the primary, secondary, and tertiary indication in our last series of cesarean sections. It is obvious that even though the patient has a contracted pelvis, if the baby is premature or very small, dystocia no longer becomes an indication. If the patient has a normal pelvis but the baby weighs 5,000 or more grams, dystocia may be present although the patient has a normal pelvis. We have given the indications for both primipara and multipara and in almost every instance, the secondary and tertiary indications played a part, especially in patients with dystocia or toxemia or in the presence of fetal and uterine (faulty mechanism) indications. Hemorrhage was the only indication in that group.

Data in Table II represent the incidence of cesarean section during the last year. The university staff has a larger number of referred abnormal patients which may account for the increased incidence.

MATERNAL MORBIDITY

The maternal morbidity, which is based primarily on a temperature of 38 degrees or more for 2 or more days after the first postpartum day, has shown a steady decrease. In the last series, we have divided those patients with morbidity into three groups as indicated

TABLE II.—DIVISION OF PATIENTS AND OPERATIONS 1948 TO 1949

Patients	Deliveries per cent	Cesarean section per cent	Incidence per cent
University, private	31	47	7.0
University, clinic	32	30	4.5
Courtesy	37	23	3.8
Total No.	4,089	190	

in Figure 3. It is worth noting that only 5.3 per cent of the patients had temperatures of 39 degrees or more; 15 per cent had temperatures of 38 to 38.9 degrees. A group of patients (12.5 per cent) with temperatures of 38 to 38.9 degrees for only 1 day are also included. We have so few sick patients after cesarean section that the resident staff is unfamiliar with the distention, vomiting, and ileus that were formerly seen even in elective cases in which there was extensive spill of amniotic fluid, meconium, and blood into the abdominal cavity. They do not appreciate the inherent dangers of cesarean section, first from infection and secondly, from embolism.

We do not fear hemorrhage from the postcesarean uterus. All uteri are routinely packed, not too tightly, for a period of 8 hours. We do not recall any patient requiring a secondary pack. Several patients have had excessive bleeding after discharge from the hospital, necessitating curettage, but the incidence of this delayed type of postpartum hemorrhage is much less after cesarean section. One patient died on the table from postpartum hemorrhage after cesarean section for placenta previa.

Some years ago we attempted to formulate a better method of reporting morbidity in patients with cesarean section. Many patients have no fever but do have anemia, tachycardia, and distention. We were unable to devise any workable formula. D'Esopo uses a "febrile index" which seems to depict the actual morbidity better than the usually accepted means for determining morbidity. The standard morbidity rate for his spontaneous deliveries is 4.6, mid forceps 21.8, and for section, 41.8 per cent, but the febrile indices are 12.4, 38.3, and 49, respectively; a 4 to 1 instead of a 9 to 1 difference when compared with spontaneous deliveries. The index for section is not much more than for midforceps, 38.3. Unfortunately, it involves only the temperature. We are now using it to determine its value. Our index on 25 unselected cesarean sections was 30.6; range 0 to 95.

The incidence of pulmonary embolism is greatest after cesarean section. Early ambulation beginning 24 hours after operation does not preclude the possibility of embolus as we had striking evidence in several such cases.

Anesthesia. There has been a very definite change in the use of local and spinal anesthesia in our cesarean sections during the past few years. In the first 1,500 cesarean sections, local anesthesia was used in over 60 per cent of the cases and local and supplementary general anesthesia in an additional 24 per cent. The hospital staff felt that all reports demonstrated that the pregnant woman was more likely to die from spinal anesthesia than the nonpregnant. This was thought to be due to the lability of the blood pressure which reaches a maximum at term. Caudal anesthesia was used in a few cases in 1942 and 1943 but was given up because it was not satisfactory. In view of the published reports of the apparent safety of spinal anesthesia in several maternity hospitals, and especially at the Margaret Hague hospital, the senior author encouraged its use in cesarean section in 1945. The amount of procaine was constantly decreased and it was determined that an expert operator could perform a laparotrachelotomy with the use of 60 milligrams of procaine. The amount usually injected varied from 80 to 100 milligrams. Dieckmann thought that the ideal type of anesthesia would be a local with the needle introduced for continuous spinal anesthesia. In the event that the local was not satisfactory, the change could then be made to the continuous spinal anesthetic and the operation completed with the total administration of 50 to 100 milligrams of procaine in split doses.

In Table 1B are given data concerning the various types of anesthesia used. Spinal anesthesia is certainly more pleasant for the patient and for the surgeon, both for his peace of mind and also because the operation requires less time. In view of our excellent results with spinal anesthesia for both vaginal delivery and

cesarean section, it may be that it is preferable to inhalation, at least for cesarean section. However, in the past year, 6 patients were given spinal anesthetics and yet supplementary anesthesia was necessary for various reasons. We think it unfortunate that the use of local anesthesia has dropped from over 80 per cent to 7 per cent of cases. Sodium pentothal, as a supplement, was not used during the past year.

The trend has been too far to the use of spinal anesthesia, in many instances not of the continuous type, and sooner or later serious complications will occur. The senior author pointed out in his 1945 report that a spinal anesthetic, consisting of 80 to 100 milligrams of procaine, is much safer for the patient and her baby than an improperly administered inhalation anesthetic provided the surgeon cannot perform the operation under local anesthesia. The latter is still preferable in patients with toxemia, in those in shock, and perhaps in cases of premature delivery.

Since low spinal anesthesia (saddle block) was introduced in January, 1947, we have had over 5,000 patients who had this type of anesthesia. In the period from July 1, 1946, to June 30, 1949, 39 per cent of the patients who were delivered vaginally had low spinal anesthesia. We believe in its use in difficult deliveries, in premature deliveries, and when there is respiratory tract infection. We also insist that each resident be trained in its use. Obviously, it has been used in many elective cases. The only difficulties we have had with spinal anesthesia have been the headaches which occurred in approximately 10 per cent of the cases. We think at present that if competent anesthetists are available, general anesthesia is preferable to spinal so far as maternal safety is concerned. Furthermore, spinal either is contraindicated or fails in certain cases. Our only preliminary medication for inhalation anesthesia is atropine 0.0004 gram. After the baby is delivered, morphine 0.1 to 0.16 gram is given subcutaneously or intravenously. We have not used curare for relaxation. Cesarean section is a simple but major operation with two lives dependent, and it should be performed with the maximum precautions for each life.

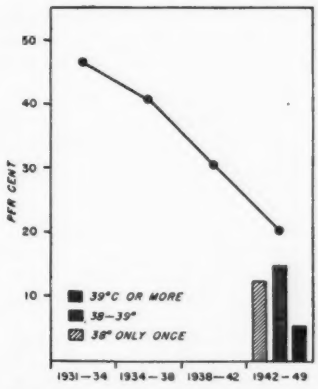

Fig. 3. Percentage of maternal morbidity in four series of cesarean sections. In the first group of patients (12.5 per cent of those from 1942 to 1949) temperature rose to 38 to 38.9 degrees C. only one day and these are not classified as morbid. Such temperature elevations would increase the febrile index.

Rupture of the uterus. Periodically, some clinic reports on a group of patients who were delivered vaginally after cesarean section. As a rule, the maternal and fetal results are good because these studies are of selected patients. However, when one realizes that if the uterus ruptured, the baby is certainly going to be lost, and that the maternal mortality with rupture of the uterus ranges from 28 to 80 per cent with an average of 40 per cent as compared with a mortality in cesarean section, as an elective procedure, of probably 0.1 to 0.3 per cent, and a fetal mortality of probably 2 per cent at the most, it seems a waste of time even to discuss the management of such cases. So far as we know, no investigator has ever made plans to deliver by the vaginal route one or more hundreds of patients who had had cesarean sections, irrespective of complications. Of course, after a cesarean section, there is always the very rare possibility of a rupture weeks or even months before term.

FETAL MORTALITY

In the majority of cases, the basic primary justification for the cesarean section is to ensure a live baby. All of us have had the experience of performing an elective cesarean section, as a repeat procedure or for dystocia, and yet of not having the baby survive. We

TABLE III.—FETAL MORTALITY

	Cesarean section				All deliveries		
	1931 to 1934	1934 to 1938	1938 to 1942	1942 to 1949	1931 to 1941		1942 to 1948
Stillbirths	2.8	2.0	2.2	1.2	400 gm.+ 5.2	1000gm.+ 4.3	1000gm.+ 1.2
Neonatal	3.4	5.2	7.0	4.7 (3.6)[b]	4.8	4.0	1.2 (0.8)[b]
Total	6.2	7.2	9.2	5.9	10.0	8.3	2.4
Premature deaths, per cent	81	73	87[a]	57	59.0	51.0[c]	61

1931–1942 include fetuses 400 gm.+
1942– include fetuses 1,000 gm.+
a—30% previable
b—omitting malformations and erythroblastosis
c—fetuses 1,000 gm.+

have 1 patient who has had 2 consecutive cesarean sections, each for the sake of a live baby, and yet in both instances the baby has not survived and the autopsies have not revealed any pathologic condition sufficient to account for the death. In our first 1,500 cases of cesarean section, all instances of abdominal delivery in which the fetus weighed 400 grams or more were included. In the last 1,371 cases the lower limit was 1,000 grams or more. Our data for fetal mortality in all deliveries and following cesarean section are given in Table III. The uncorrected fetal mortality, in which antepartum death from abruptio placentae and toxemia are included, is much higher than the total hospital mortality.

There has been a constant decrease in the hospital stillbirth and neonatal rate during the 18 year period. The stillbirth rate in cesarean section is much less in the last series, but the neonatal rate is still higher than the hospital rate. It is obvious that the fetal loss after cesarean section is definitely greater than the hospital rate which includes the figures on cesarean section. Some of the deaths are due directly to abruptio, placenta previa, and indirectly to prematurity resulting from the former conditions as well as from toxemia. Some of the premature deaths apparently are due to an increased amount of fluid in the meninges and fibrin deposit in the lung alveoli, a condition which we call Potter's disease.

The neonatal death rate among the last 1,371 deliveries by cesarean section in infants weighing over 1,000 grams is 4.7 per cent. If those infants with major malformations and erythroblastosis are omitted, the death rate is 3.6 per cent. During the same period, the neonatal death rate for live-born infants in the hospital was 1.2 per cent, and if the number of those dying from malformations or erythroblastosis are omitted, it is 0.8 per cent. Thus in cesarean section, a life-saving operation for the baby, the mortality for the baby is over four and a half times that for the hospital as a whole. Fifty-seven per cent of the total deaths in infants delivered by cesarean section were in those weighing less than 2,500 grams. To reduce the fetal mortality, the obstetrician must concentrate his efforts primarily on this latter group. The duration of pregnancy must be as long as possible; the test of labor must not be carried to undue lengths; the anesthesia must be one favorable to the fetus—local, spinal; blood loss from the mother must be minimized; as much blood as possible must be permitted to escape from the placenta into the baby. The senior author routinely leaves the umbilical cord long if the baby is premature and immediately after operation injects 20 to 30 milliliters of citrated mother's blood into the umbilical vein. If the fetus is premature, or its condition is not good, it should be placed in an observation or a premature nursery where it can be given oxygen, parenteral fluids, proper nursing care, and breast milk in adequate amounts.

The fetal deaths in the first 1,000 consecutive cesarean sections were studied by Potter. The different maternal indications for cesarean section are given in Table IV. Placenta previa, abruptio placentae, and toxemia were responsible for 41 per cent of the deaths. In toxemic patients delivered by cesarean section the mortality for fetuses weighing 1,000 grams or more for the period 1939 to 1948 was 8.4 per cent, and for fetuses weighing 1,500 grams or more was 7.8 per cent.

COMMENT

Cesarean section has always been a recognized procedure, but it has only been within the past decade that the operation has become so safe that the indications have been increased. It must never be used as the "last resort" operation. Such operations resulted in the ap-

palling mortality of 10 to 50 per cent. It is in this type of patient that any major operative procedure frequently ends fatally. D'Esopo has recently discussed the trend in cesarean section and has demonstrated that in their clinic, cesarean section is replacing difficult mid forceps delivery and is used in the delivery of abnormal positions with a decided decrease in the fetal mortality and not only no increase but in some cases an actual decrease in the maternal mortality. Our experience has been a similar one. If we had an exact method for determining the weight of the baby within 5 to 10 per cent, we would perform a few more operations in patients in whom the baby weighs over 4,200 grams or the mechanism of labor is faulty; yet, because the patient has a normal pelvis, undue chances are taken in the delivery of occasionally very large babies.

The treatment of the patient in whom potential or actual infection is present is also changing. Several clinics, including ours, have favored cesarean hysterectomy in this type of patient if the baby was undamaged. Several other clinics, and especially the Margaret Hague staff, have favored the extraperitoneal cesarean section. D'Esopo, in his recent report as well as in a personal communication, states that they have not performed the extraperitoneal cesarean for over 5 years. They are not performing cesarean hysterectomy. They administer the antibacterial drugs very early in labor and continue them into the puerperium. They have had 1 death from intestinal obstruction and secondary peritonitis in 1,000 consecutive operations. Douglas, at the New York Hospital, apparently still performs some extraperitoneal sections, but he also believes that the early and intensive administration of penicillin, sulfadiazine, and other antibacterial agents throughout labor and the puerperium will minimize the dangers of prolonged rupture of membranes not only to the mother but also to the fetus. Prolonged labor causes an increased fetal mortality from asphyxia, brain hemorrhage, and infection. These observations are striking since most of the evidence indicates that these various antibacterial drugs have little or no effect on the usual anaerobic cocci which cause most of the puerperal infection in these patients. Since our results with the use of these substances in vaginal deliveries have not been so striking we have not used them in the treatment of patients following cesarean section.

TABLE IV.—FETAL MORTALITY IN CESAREAN SECTIONS

Indications	1931–38 per cent	1939–48 per cent
Cephalopelvic disproportion	1.4	
Elective: previous cesarean or for fetal causes	1.7	
Maternal hemorrhage	19.2	
Toxemia of pregnancy	22.0	8.4
Cardiac disease	3.8	
Other organic diseases	6.4	

In view of the results reported, however, we also will use these substances in treating our patients with prolonged rupture of membranes or prolonged labor and will slowly increase the duration of our presumably "clean cases." *We believe that these studies should be limited to the large clinic services until more experience has been gained.* The doctor performing the few cesareans each year, incidental to private practice, should adhere to the rules outlined by Dieckmann in 1945.

CONCLUSIONS

Cesarean section performed by a properly trained obstetrician is now a recognized procedure for the management of many obstetric and fetal complications formerly treated by vaginal delivery because the maternal mortality, attributable to the operation itself, is only 0.1 per cent or less. The fetal mortality, ascribable to the operation, is less than 1.0 per cent.

Spinal anesthesia, especially of the continuous type, is better for the baby than any type of anesthesia except local. Generally speaking, it is apparently not as safe for the patient as inhalation anesthesia if the latter is given by a trained anesthetist after careful preparation.

Despite reports from other clinics about the safety of the extraperitoneal cesarean section or low cervical operation with antibacterial drugs, we still follow the practice previously described unless any of the following contra-

indications are present: (1) ruptured membranes or labor of over 24 hours; (2) repeated rectal or vaginal examinations; (3) operative manipulation either for induction of labor or for delivery; (4) uterine infection; (5) a damaged or dead fetus; (6) assurance of a lower maternal mortality by another procedure, usually a craniotomy.

Death from peritonitis or bacteremia after cesarean section as an elective operation or after a short test of labor must be charged to the obstetrician and the operating room staff. All methods used for sterilizing solutions, instruments, gloves, drapes, and packs must be checked periodically by the use of living bacteria. The operating room technique must also be watched for carelessness and for improper changes.

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CYTOLOGIC DIAGNOSIS OF MALIGNANT DISEASE IN A GENERAL OFFICE PRACTICE

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IN recent years great interest has been focused on the diagnosis of early cancers by cytologic studies (2, 3, 5, 6, 8, 9). Advocates of such methods have found these particularly valuable in the early diagnosis of uterine cancer which might escape early detection by other more conventional means (3), and reports are now available in which these methods seem definitely advantageous in the diagnosis of early cancer in other areas of the human body (1, 4, 10, 11).

Our study was prompted by the fact that this laboratory was afforded an opportunity to evaluate the method in a fairly large and nonselected office population coming to practitioners' offices and, at the same time, to study and evaluate the pitfalls of the method in a general hospital laboratory. Simultaneously, an attempt was made to determine the value of cytologic methods in the diagnosis of early cancer which might escape detection by conventional histological procedures. Thus, it appeared that ultimately we might draw some definite conclusions with regard to the advisability and practicability of using cytologic diagnostic methods to detect early malignant disease.

The report presented here is based on a study made in our laboratory from January 1, 1948 through May 7, 1949. The need for this study as well as the service it provided was seen in the fact that many doctors in the area which this laboratory serves had previously become accustomed to taking routine vaginal smears on their patients as a part of their routine examination. The smears were then examined by the State Tumor Diagnosis Service which, however, had to discontinue this service in 1947. Thus, in one series of about 2,000 routine examinations, at least 3 unsuspected cases of cancer were detected (7).

The report is based primarily on the examination of smears from the vaginal vault. A few smears obtained by aspiration of material from the breasts or by secretions from the nipple are also available. With very rare exceptions, all smears were obtained from patients entering the practicing physician's office for a general physical examination. For fixation of smears, the method recommended by Papanicolaou was used. The smears were then sent to our laboratory and stained according to Papanicolaou's method. Very little, if any, clinical information was usually available to the examiners. The report thus represents a survey made on patients in a general office practice who in the majority of instances were not primarily suspected of having cancer.

Since our study was the first attempt of this laboratory to make a diagnosis from cytologic material obtained from office patients, and since it was different from the cytologic examinations ordinarily carried out in a histopathological laboratory, preliminary studies seemed advisable to familiarize the examiners with the pitfalls of the diagnosis from cytologic smears. Textbooks on the subject, references in the literature, photographs and smears obtained from hospitalized patients with known cervical or endometrial cancer, as well as negative patients, were used. In the beginning of the study, i.e., for the first 6 months, the pathologist of the laboratory screened and diagnosed all cases submitted. Later, the junior author interested in the subject and trained in a similar fashion took over this task. A technician was employed to do the technical work but was used only in a limited way to do some screening.

In the study of this material, an average of 10 minutes was spent in the examination of

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TABLE I

	No. cases	Per cent
Total cases	1,721	....
Negative cases	1,674	97.3
Cases first reported positive	47	2.7

each individual smear. As the number of smears sent to the laboratory increased, it was necessary to spend an average of from 2 to 3 hours per day on the reading of the smears. A part-time secretary was charged with the reporting of the findings as well as filing and cross indexing of the results.

The time factor ultimately became the major problem of the study. Lombard, Middleton, Warren, and Gates state: "Once the necessary training has been gained, a technician can read between 20 and 40 smears per day." This would average 12 minutes per smear provided no other duties are performed by the technician. In our study, it became evident that this number of smears was somewhat too large for one person to examine because as the day went on, accuracy definitely suffered in the screening and examination of slides, possibly because of eye fatigue. An important additional problem confronting us as well as those in any general hospital laboratory was that other duties of the professional staff frequently precluded the assumption of duties consuming as much time as this problem required. Therefore, it became obvious that the professional personnel in the long run could not examine all the smears sent to the laboratory, and for this reason it would be necessary to train technicians in the performance of this duty. There appears little doubt that a well trained technician with some cytologic background can be adequately trained to screen and even to diagnose a cytologic smear. It is anticipated that in this laboratory such screening will be performed by technicians but the ultimate diagnosis of a malignant smear will rest with the professional staff who act as the final authority on the subject. From the experience gained in this laboratory it would appear that from 4 to 6 months would be necessary in order to train a technician, who was previously inexperienced in this field but who has some background in histology, to perform the necessary duties thoroughly and accurately.

TABLE II

	No. cases
Cases first reported positive	47
Positive smears confirmed by biopsy or curettage	26
Positive smears not available for follow-up but confirmed by other cytologists	2
False positive because of postirradiation effect	1
Cases reported positive by smear but found negative by biopsy or curettage	8
Cases first diagnosed as positive but not available for follow up	10

ANALYSIS OF CASES

In the period of January 1, 1948 to May 9, 1949, a total of 1,721 cases came to our attention. The number of smears examined was between 1,900 and 2,000. The majority of smears were vaginal (3 were breast smears), a few were made directly from the cervix, and all were taken on the patient's first visit to the doctor's office. Of the entire series, 47 cases were reported positive, or a total of 2.7 per cent and 1,674 cases were reported as negative. An attempt was made to follow up all cases, but this was possible only in a fraction of those cases reported negative (Table I).

In analyzing the 47 cases reported as positive, 26 were confirmed as malignant by biopsy, curettage, or other conventional histopathological methods, 2 patients did not avail themselves of further examination. The smears obtained from these 2 patients were sent to other cytologists and the diagnosis made in our laboratory was confirmed. One case brought to the laboratory early in the investigation was reported as positive and was ultimately found to come from a patient in whom carcinoma of the cervix of the uterus had been irradiated 11 years previously. At this time, no evidence of carcinoma was found clinically or by biopsy. Eight cases were proved negative by biopsy or curettage and the 10 remaining patients did not avail themselves of further examination (Table II).

As time went on and with the experience gained in our study, it became obvious that mistakes in interpretation and diagnosis made earlier could now be avoided. This led to a rechecking of all our positive smears recently. On review, all smears previously reported as positive and confirmed by biopsy or curettage were again so diagnosed. Special attention was paid to the 10 cases in which no follow-up

TABLE III.—REVIEW OF CASES REPORTED POSITIVE BUT NOT FOLLOWED UP FURTHER

Number cases	Original diagnosis	Diagnosis on review
7	Positive	Papanicolaou Class III
3	Positive	Papanicolaou Class II
2	Positive	Papanicolaou Class V

was available. On review, 3 of these were now considered negative and all 3 had been first viewed in the early days of the study. The remaining 7 cases were now considered doubtful or classified in Class III as suggested by Papanicolaou. Because none of the patients from whom these smears were taken was available for a follow-up, no conclusions as to accuracy on the final diagnosis of these smears is possible.

Table III definitely demonstrates the necessity of prolonged and continued specialized training for the correct interpretation of cytologic smears.

Table IV illustrates the site of the cancer in the 26 cases of proved carcinoma. Thirteen (50 per cent) were squamous cell carcinoma of the cervix uteri, 10 (38 per cent) were adenocarcinoma of the corpus uteri, and 3 (12 per cent) were carcinoma of the breast.

TABLE IV

	No. cases	Per cent
Carcinoma of the cervix uteri	13	50
Carcinoma of the corpus uteri	10	38
Carcinoma of the breast	3	12

COMMENT

This study leaves little doubt that considerable experience is necessary before adequate and accurate diagnosis can be guaranteed. It also becomes obvious that the primary responsibility for the examination and possible screening of all cytologic smears must be shifted from purely professional personnel to responsible and adequately trained technicians. While it appears definitely advisable that the ultimate diagnosis of a malignant smear rest with a physician trained in cytology, it seems hardly possible to find the necessary professional staff to carry on this exclusive task. In fact, it might even become a major task to recruit a sufficient number of skilled technicians, should the method become firmly established as a means of screening and diagnosis.

The results obtained in the survey would serve to indicate that once experience has been gained, accuracy in diagnosis becomes fairly dependable. While little harm may be done in reporting a smear positive, even if biopsy or curettage fail to show any evidence of cancer, a negative report on a smear coming from a patient suffering from malignant disease would be a definite fallacy. It is for this reason that in reporting our findings to physicians, we drew attention to the fact that a negative report did not exclude cancer and that history, clinical findings, and other means of diagnosis should exclude such a possibility. Therefore, it seems to us that while there is a definite value in cytologic methods of diagnosing malignant disease early, they should still be regarded as an aid in the diagnosis and not as a diagnosis in themselves. Their great value seems to lie in their availability in the office, the ease with which the smears can be prepared, the rapidity with which an initial interpretation is possible, thus preventing or hastening hospitalization of the patient for further biopsy or curettage and the relatively low cost of the procedure.

In this report, no attempt is made to evaluate the ultimate accuracy in diagnosing cytologic smears, since most of the cases reported as negative could not be followed further. This in itself precludes valuable statistical information.

However, the fact that in a series of 1,721 patients entering a doctor's office and in most instances seeking consultation, not because of indication of cancer, but for a general checkup, 47 were considered suspicious and 28 actually found to be suffering from malignant disease would not only seem to warrant the continuation of such a service to the physician and the patient, but also to make it mandatory for the pathologist to familiarize himself thoroughly with these methods of diagnosis. There would appear to be little doubt that in our era of cancer consciousness all new laboratory aids in the diagnosis of malignant disease should be thoroughly studied and evaluated by the pathologist and that these should be provided to the patient if they are found to be of value.

SUMMARY

Cytologic smears made from 1,721 female patients in a general office practice resulted in the finding of 28 proved cases of malignant disease and cast suspicion of malignancy on 10 other cases. In this study, the necessity for shifting responsibilities for screening from professional to technical personnel was demonstrated.

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MYOCARDIAL INTOLERANCE TO EXCESSIVE BLOOD TRANSFUSION

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THE administration of blood to surgical patients, with the proper indication, has without doubt been one of the significant advances in the preoperative preparation of patients, operative surgery, and postoperative care in the past three decades. The enormous volume of research performed on blood groups, pyrogens, anticoagulants, and direct and indirect transfusions has made possible the universal acceptance of this procedure. Blood banks established within the past few years in so many hospitals in this country have made available relatively large quantities of blood. No one can deny that the ready availability of blood for transfusion has been one of the major factors permitting surgeons to extend operative procedures, especially for cancer, to degrees that 30 years ago would have been considered, to say the least, ill advised.

We have observed during the past few years that some surgeons use blood indiscriminately. The considered contemplation given a prospective transfusion as short a time as 15 years ago is not frequently encountered today. The accessibility of large quantities of blood has prompted its injudicious and unnecessary use, especially during the course of an operative procedure. A policy of preventing shock from blood loss by meticulous hemostasis and the appropriate use of intravenous blood is wholeheartedly to be commended, but not when the principal reliance for such prophylaxis is on excessive quantities of blood. If a rather sudden increase in the effective circulating blood volume and the oncotic pressure of the blood were not harmful, we would be less concerned about the administration of several liters of blood. We have reason to believe, however, that many patients are not benefited in these circumstances. We have seen several patients die as a result of what was considered to be the overly enthusiastic use of blood. These patients have clinically presented evidence of hypotension which became progressively worse as more blood was given. Cyanosis, distention of the superficial veins, and preoperative evidence of a damaged myocardium were also observed. At postmortem examination, a large dilated heart, a remote myocardial infarct or severe arteriosclerosis of the coronary arteries, and venous distention have been the only constant findings. Evidence of an acute myocardial infarction has been lacking.

An abbreviated history of one of the patients follows:

A 69 year old white male was admitted to University Hospitals with a recent weight loss of 10 pounds. Eight years previously he had been hospitalized for 4 weeks with a "ruptured vessel of the heart" and associated chest pain and dyspnea. During the interval between the two admissions he had complained of intermittent precordial pain induced by effort or excitement. Physical examination showed a blood pressure of 165/108, pulse 100, respirations 20, and temperature 36.8 degrees C. The heart was enlarged to the left by percussion. There were no murmurs and a normal sinus rhythm was present. The liver was palpable 4 centimeters below the right costal margin. Peripheral arteries were tortuous. The blood hemoglobin was 74 per cent, red blood count 4.1 million, white blood count 13,700, Wassermann negative. Serum proteins were 6.8 grams per 100 cubic centimeters, albumin 3.6 grams per 100 cubic centimeters, and globulin 3.2 grams per 100 cubic centimeters. Blood urea nitrogen was 18 milligrams per 100 cubic centimeters and plasma chlorides 585 milligrams per 100 cubic centimeters. Urinalysis was normal. An electrocardiogram was reported as an "abnormal record showing left ventricular hypertrophy." Roentgenographic examination of the gastrointestinal tract showed a neoplastic lesion in the esophagus.

The patient was taken to surgery for resection of the neoplasm. A nitrous oxide-oxygen-ether anesthesia was administered. The procedure began at 9:10 a.m., and blood was started intravenously at 9:50 a.m. During the course of the operation the

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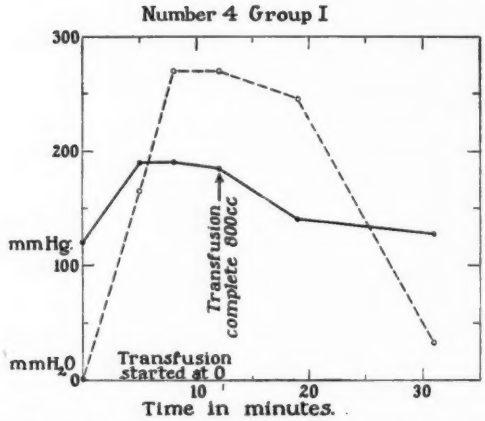

Fig. 1. · ——— · , Carotid pressure; ◦ - - - - - ◦, central venous pressure. Example of pressure changes in 1 experiment in the control group.

patient received 3,500 cubic centimeters of whole blood and 300 cubic centimeters of normal saline. This amounts to 11.6 cubic centimeters of blood per minute. During the procedure the blood pressure varied from 110/90 to 210/135, and the pulse pressure from 20 to 75. The pulse rate fluctuated between 95 and 140. At 4:00 p.m. the patient returned to the ward. His blood pressure was 120/110, pulse 126, and weak, and respirations 36. He was cyanotic and superficial veins were distended. He was given inhalations of oxygen under positive pressure. Between 4:15 and 5:20 p.m. the pulse rate remained at 130, respirations varied from 32 to 38, and the blood pressure was recorded at 166/104, 190/130, and 178/120 at 15 minute intervals. After 5:15 p.m. no blood pressure could be recorded, the pulse became imperceptible and expiration occurred at 5:30 p.m.

Observations made during the course of the operation indicated that there was only a small amount of blood lost and not nearly enough to require 3,500 cubic centimeters for replacement.

A postmortem examination showed arteriosclerosis with stenosis of the coronary arteries, a healed myocardial infarction of the posterior and lateral walls of the left ventricle, acute passive hyperemia of the lungs, edema of the lungs, acute passive hyperemia of the brain, acute hyperemia of the kidneys, and chronic pyelonephritis.

The circumstances under which this and other patients succumbed led us to attempt to determine in the laboratory whether dogs having a damaged myocardium tolerated large quantities of blood less satisfactorily than dogs with a normal myocardium.

METHOD

Blood was obtained from normal dogs anesthetized with intravenous sodium pentobarbital 0.030 gram per kilogram. The femoral and carotid arteries were cannulated and the blood allowed to run into a 2 liter bottle. The blood was maintained in an incoagulable state by adding 30 milligrams of heparin to 2,000 milliliters of blood. Blood was always used for transfusion within 30 minutes after its withdrawal.

The dogs used for the experiments were healthy mongrels weighing between 5 and 15 kilograms. For each operative procedure they were anesthetized with intravenous sodium pentobarbital. Groups II and III, subsequently described in more detail, had the left anterior descending coronary artery doubly ligated with silk. Endotracheal mechanical respiration was maintained during these operations. Prior to each experiment a siliconated cannula was inserted into the left carotid artery, and partially dampened blood pressures were recorded by a mercury manometer on a smoked drum. A siliconated brass cannula 15 centimeters in length was inserted through the left jugular vein into the superior vena cava, and central venous pressures were recorded on the smoked drum. A No. 16 cannula was inserted into the left femoral vein immediately before starting the records, and through this cannula the blood was delivered by gravity. The total amount of blood and the rate of infusion were observed.

During the course of each experiment observations were made concerning the distention of superficial veins, cyanosis, salivation, hemoptysis, and changes in the character of respiration. Recorded were the systemic arterial and central venous pressures. Changes in the pulse rate and pulse pressure were also observed. The administration of the blood was computed in milliliters of blood per minute and milliliters of blood per kilogram of body weight.

Postmortem examinations were done on all the animals that succumbed during the acute

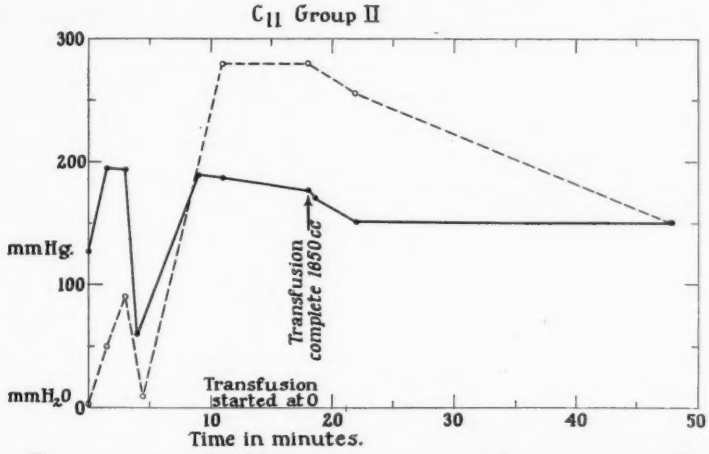

Fig. 2. · ——— · , Carotid pressure; ∘ – – – – – ∘, central venous pressure. Example of pressure changes in 1 experiment in the group of animals with small left ventricular infarcts. The temporary reduction in both pressures shortly after the onset of the transfusion is demonstrated.

experiment, and those animals that survived were sacrificed by injecting 20 cubic centimeters of sodium pentobarbital, 6 per cent solution, intravenously. Postmortem observations were made with reference to pericardial adhesions, dilatation of the heart, the site of coronary ligation, and the size of the myocardial infarct in the left ventricle. Also noted were the degree of passive hyperemia in the lungs, liver, and spleen; pulmonary and intraperitoneal hemorrhage; serosanguineous fluid in the peritoneal cavity; and the extent of petechial hemorrhages in the gastrointestinal tract.

The animals were divided into Groups I, II, and III. Group I consisted of 5 animals that were subjected to no previous operative procedure. Group II comprised 7 animals that had had the left anterior descending coronary artery ligated just distal to the first large branch 1 month prior to the time observations on the blood transfusion were made. These dogs had recovered from the coronary artery ligation without any complication and at the time of the experiment were apparently in good health. Five animals made up Group III, and these were similar to the dogs in Group II except that the left anterior descending coronary artery was ligated at its origin from the circumflex coronary artery.

OBSERVATIONS

The animals in all three groups exhibited certain similar hemodynamic changes. Within a few seconds after starting the blood transfusion, the blood pressure rose 30 to 70 millimeters of mercury. The pulse rate increased slightly or remained essentially the same. The pulse pressure increased variably from 4 to 40 millimeters of mercury, but in general it became three to four times the pretransfusion figure. Over a period of 5 minutes the central venous pressure rose progressively to levels above 27 centimeters of water which was the maximum level that could be recorded on the kymograph used in these experiments. In Group I the central venous pressure remained elevated until the administration of blood ceased. It then returned to the original level over a period of 5 to 15 minutes. In this group the arterial blood pressure also returned to normal (Fig. 1). Two of these dogs were sacrificed 30 minutes after completion of the experiment, and 3 were allowed to recover from the anesthesia. The following day 1 animal died. The other 2 were lethargic, but within the next 5 days they appeared to recover completely.

The central venous pressure and arterial pressure responded in a similar fashion in Group II (Fig. 2), the animals with small areas

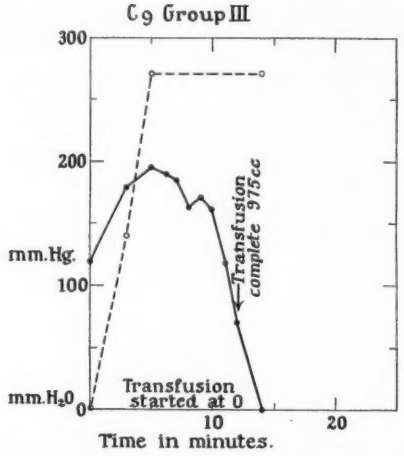

Fig. 3. · ——— · , Carotid pressure; ∘– – – – ∘, central venous pressure. Example of pressure changes in 1 experiment in the group of animals with large left ventricular infarcts. The central venous pressure remained high until death intervened.

of myocardial infarction. Both pressures returned to pretransfusion levels as promptly as in the first group. One difference in the recording of pressures in this group was observed. Shortly after the central venous pressure reached levels of 10 to 20 centimeters of water above the initial level there was a sudden drop of both venous and arterial pressures to low levels. Recovery occurred over a period of 5 minutes, and the pressures resumed their high levels. This could not be explained during the experiment, but the postmortem examination after the animals were sacrificed showed several hundred cubic centimeters of blood free in the peritoneal cavity. This did not occur in Group III.

The same hemodynamic changes were observed in the third group of animals having a large left ventricular infarct. The consistent difference was that the central venous pressure never fell, and the systemic arterial pressure fell progressively until death intervened at various intervals up to 31 minutes after the start of the transfusion (Fig. 3).

During the course of the experiment in all groups, distention of the superficial veins and cyanosis of the mucous membranes occurred. Salivation and hemoptysis were marked in the animals with large left ventricular infarcts and

TABLE I.—AUTOPSY FINDINGS

	Myocardial infarction	Free blood peritoneum	Pulmonary hemorrhage	Hepatomegaly	Splenomegaly
Group I					
Exp. 5	∘	2+	∘	3+	3+
Exp. 6	∘	Not sacrificed			
Exp. 4	∘				
Exp. 1	∘				
Exp. 7	∘	3+	2+	3+	
Group II					
C-1	2+	4+	2+	3+	4+
C-2	1+	4+	2+	3+	3+
C-4	∘	4+	∘	3+	3+
C-5	∘	4+	∘	3+	3+
C-6	1+	2+	∘	4+	∘
C-7	∘	3+	2+	∘	∘
C-11	1+	3+	1+	4+	2+
Group III					
C-3	4+	∘	3+	3+	3+
C-8	4+	∘	3+	3+	∘
C-9	4+	∘	3+	3+	∘
C-10	4+	∘	4+	4+	1+
C-12	4+	∘	4+	4+	3+

practically absent in the control animals. The respiratory rate and volume varied considerably but in general both increased while the blood was being infused. In Group III the respiratory rate became slow as the animals developed the terminal hypotension.

The postmortem examination of the animals that either died during the experiment or were sacrificed afterward displayed many findings that might be anticipated in an animal whose blood volume has suddenly been increased two to three times normal (Table I). In Group I the heart showed nothing unusual except a moderate dilatation of all four chambers. Only 2 of the 5 animals in this group were sacrificed. There was no gross pulmonary hemorrhage in one animal and a few focal areas in the other. There was a moderate passive hyperemia of the liver and spleen and numerous petechial hemorrhages in the submucosa and subserosa of the gastrointestinal tract. A small amount of serosanguineous fluid was found in the peritoneal cavity. No cerebral hemorrhage had

TABLE II.—DATA ON THE QUANTITY AND RATE OF BLOOD TRANSFUSED

Exp. No.	Weight of dog kgm.	Total amount of blood ml.	Time of transfusion min.	Ml. of blood per kgm. of body weight	Ml. of blood per min.
Group I. Control animals—lived					
1	9.5	500	23	52	21
4	10.0	800	12.5	80	64
5	7.3	900	19	123	47
6	10.0	900	20	90	45
7	7.0	1000	26	142	38
			Average	97	43
Group II. Small to moderate myocardial infarcts—lived					
C1	7.7	1175	21	152	56
C2	8.0	1850	47	231	39
C4	8.7	1750	25	201	70
C5	12.3	1400	21	113	67
C6	12.4	1200	21	96	57
C7	15.2	1800	24	118	75
C11	6.7	1600	18	238	89
			Average	164	69
Group III. Large myocardial infarcts—died					
C3	10.0	1200	31	120	38
C8	5.8	1200	21	206	57
C9	5.7	975	12	171	81
C10	6.3	1450	21	230	69
C12	9.3	1650	16.5	177	100
			Average	181	69

occurred. The veins of the subcutaneous tissue of the abdominal wall and those of the mesentery were distended.

The animals in Group II all showed fibrous adhesions between the pericardium and epicardium which were most dense in the vicinity of the coronary ligation. The site of ligation in each animal was reidentified by dissecting out the silk sutures which had been previously used to effect occlusion of the coronary artery. In 4 of the 7 animals in this group an infarct measuring approximately 1 centimeter in diameter was identified near the tip of the left ventricle. In the other 3 animals occlusion of the coronary artery was demonstrated, but obvious collateral anastomoses from the right ventricle had prevented the development of an

Fig. 4. A transection of the left ventricle near the apex, dog number C3, Group III, showing the destruction of the myocardium and its replacement by fibrous connective tissue on the upper side of the photograph.

infarct in the left ventricle. All of the hearts displayed a moderate dilatation. Gross pulmonary hemorrhage in focal areas was present in 4 animals and absent in 3. In 2 of 3 showing no pulmonary hemorrhage no myocardial infarct was found; in the third the infarct was small. Intense passive hyperemia of the liver and spleen were observed in all but 1 of the animals. Petechial hemorrhages were numerous throughout the gastrointestinal tract. In each of these animals at least 200 milliliters of free blood were found in the peritoneal cavity. No source for the bleeding could be identified. Distention of the mesenteric and subcutaneous veins was apparent.

The third group, consisting of 5 animals that died during the experimental procedure, showed, at necropsy, findings in the heart and pericardium similar to those in the previous group except that all 5 had an infarct at least 2 centimeters in diameter near the apex of the left ventricle (Fig. 4). The infarct was characterized by complete replacement of the myocardium by a thin sheet of translucent fibrous tissue. All of these hearts showed enormous dilation. The lungs showed intense passive hyperemia and large areas of diffuse hemorrhage. Passive hyperemia of the liver was severe but only moderate in the spleen. Subcutaneous veins were distended, but mesenteric veins, in contrast to the two previous groups, were not unusually distended. Petechial hemorrhages in the gastrointestinal tract were infrequent and in no animal was free blood found in the peritoneal cavity.

DISCUSSION

These experiments, we believe, demonstrate in a relative fashion that a heart whose myocardial reserve is reduced will not tolerate the load placed upon it by a circulating blood volume that has increased rapidly. It is difficult and perhaps unwise to draw conclusions from these experiments that may be unequivocally transferred to clinical surgery. It is true that the amount of blood and rate of infusion in this work would rarely be encountered in clinical practice except in profound hemorrhagic shock. It is equally true, on the other hand, that many human hearts which might be subjected in certain circumstances to a rapid increase in circulating blood volume do not have an isolated area of myocardial fibrosis but diffuse atheromatosis of the coronary arterial tree. It may be presumed that considerably less blood, relatively speaking, than was used in these experiments might produce the same results in a human whose myocardium is affected by diffuse vascular disease.

The control group of animals did not receive as much blood as the second and third groups; nor was it administered as rapidly. The second and third groups received comparable amounts of blood per kilogram of body weight, and the average rate of administration was identical for both groups (Table II). It is felt that Group II served as an adequate control for Group III since the experiments were identical save for the size of the myocardial infarction. The most impressive observation was, of course, the death of the animals in Group III in a state of progressive hypotension, bradycardia, and elevated central venous pressure. In addition, however, the animals in this group experienced marked pulmonary hyperemia and hemorrhage and no free blood in the peritoneum. These findings were reversed in Group II and suggest myocardial failure of the left ventricle in the animals in Group III with the large area of fibrosis.

Besides the death of the animals with large myocardial infarcts it was noteworthy that the normal animals and those with small areas of myocardial infarction could tolerate the tremendous increases in blood volume to which they were subjected and display relatively normal pressure relationships shortly after cessation of the infusion.

CONCLUSIONS

The blood transfusion is one of the most important tools available for reducing the risk of surgery, but its use as a prophylactic measure against operative shock, which may not and in most instances should not exist, is not to be condoned. Animals with damaged myocardia will not tolerate large quantities of blood.

Our observations, clinical and experimental, suggest that many patients with diffuse coronary arteriosclerosis do not have sufficient myocardial reserve to withstand the rapid increase in circulating blood volume that the administration of several liters of blood entails.

FOOT PROBLEMS IN CHILDREN

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IT is necessary to understand the common foot problems in children in order to be able to treat and to give advice concerning the various conditions. Mothers are conscious of their children's feet and they seek information to protect the little patients from the present day rampant exploitation by advertising agencies, shoe salesmen, and other unqualified nonprofessional groups. To simplify the subject of the care of the feet this paper has been prepared from a practical standpoint, limiting the discussion to diagnosis and treatment, without mention of theory, etiology, or unnecessary details.

Pronated foot. This term is reserved for feet which present a good longitudinal arch but which show an internal rotation of the foot upon standing (Fig. 1). The condition is the most common foot problem in children. It is referred to frequently as "weak ankles," because of the medial inclination of the foot and tibia with prominence of the medial malleolus, giving the impression that the ankle joint is weak but such is not the case. Also, it is confused with weak foot and flat foot but can be differentiated from these by placing the patient in a standing position and passively rotating the foot back to a normal position beneath the tibia. In Figure 1 the foot on the left is in a typical pronated position but on the right for comparison the patient is holding the other foot in a corrected position. It is noted that the longitudinal arch remains unchanged in height and that the pronated foot merely has rotated inwardly at the talocalcaneonavicular joint. Since the longitudinal arch is normal, correction can be obtained by forcing the rearfoot back into position through the use of inner heel wedges of 1/8 inch, changed to 3/16 inch when the child is older, plus exercises designed to strengthen the anterior and posterior tibial muscles. This exercise is done best by rising on the toes and then slowly rolling down the outer border of the feet until the heels reach the floor, the patient contracting the anterior and posterior tibial muscles during the procedure. The prognosis in such cases is good.

Weak foot. This condition is one in which the longitudinal arch of the foot is relaxed. Other names applied to the same deformity are flatfoot, flexible foot, strained foot, and static foot. In Figure 2 on the left the longitudinal arches are seen to be relaxed while on the right the patient is attempting to elevate the arches but is unable to do so completely which is in contradistinction to, and the differential diagnostic point from, pronated feet (compare with Fig. 1). In addition to the longitudinal arch being decreased the dorsiflexion of the foot is 15 to 30 degrees less than a right angle. Most children are born with such findings but the feet of about one-half will develop normally without treatment. Inasmuch as it cannot be determined in advance which group will develop normally it is wise to do nothing until the child begins to walk. Should the findings persist a prescription should be given for wedges of 1/8 inch on the inner heel and 1/8 inch on the outer sole. When the child is three or more years of age the inner heel wedges should be 3/16 inch in height. Since the longitudinal arch is relaxed the purpose of the wedges is to rotate the rearfoot outward and the forefoot inward to re-establish the arch. Upon walking, the arch is locked in a corrected position, and at the same time the musculature of the foot is used normally as opposed to the artificial support gained from the use of metal, rubber and leather arches, scaphoid pads and Thomas heels. The child should not be allowed to go barefoot for any extended period of time. The prognosis in such cases is fair.

Talipes calcaneovalgus. This condition is a severe form of weak foot, being congenital in type, and frequently ending in a flat foot. Dorsiflexion of such feet often is 30 to 45 degrees less than a right angle, and may be suffi-

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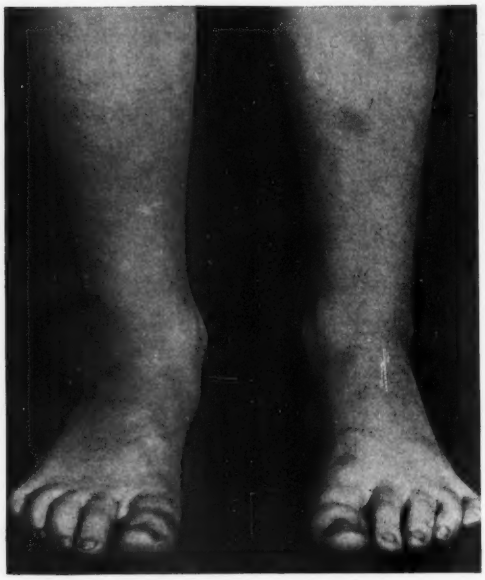

Fig. 1. Pronated feet. Note typical internal rotation of foot on the left, while on the right patient is correcting the rotation showing that the longitudinal arch is normal. Compare with Figure 2.

ciently severe to allow the dorsum of the foot to be pushed up and against the tibia, making the calcaneus prominent as is seen in Figure 3. At the same time the foot is everted producing valgus and pronation (Fig. 4). Academically the condition belongs to the family of clubfeet but this term should never be used to the layman because it stigmatizes the child for life when, in reality, the condition is nothing more than a severe type of weak foot. Often at birth such feet are fixed in dorsiflexion and eversion, causing alarm to the mother, but they may well be left alone or for reassurance, the mother may be told to stretch the feet downward each time the diapers are changed. The use of plaster of Paris, wedging casts, braces, and splints are of no more value than passive stretching; in fact, without any treatment the feet will resume a normal position at rest. Inasmuch as the longitudinal arch is severely relaxed it is necessary upon walking to support the entire inner border of the foot through the use of inner heel and inner sole wedges. According to the degree of deformity the wedges vary from 1/8 to 3/16 inch in height although if the condition is mild the same treatment described above for weak feet may be employed, with or without scaphoid pads. In either case no promises of cure should be made for the prognosis is poor, because the congenital type of weak feet do not develop normal longitudinal arches. The use of naviculocuneiform arthrodesis (surgical fusion of the two bones at the apex of the longitudinal arch) at about 10 years of age when the bones are developed sufficiently is a well recognized procedure and is quite useful in preventing symptoms later in adult life.

Plantar flexed talus. This condition is the most severe form of weak foot and is a true flat foot. It is a congenital deformity in which the talus, or the old term "astragalus," is deviated excessively toward the sole of the foot (Fig. 5). The talus carries with it the navicular bone producing a marked flattening of the longitudinal arch. The diagnosis may be suspected if the longitudinal arch appears reversed like the rocker of a rocking chair and may be confirmed by x-ray studies of the feet in the standing position. The prognosis is poor because unfortunately the condition is not amenable to conservative measures. It is the proper case, however, in which to use arch supports in the form of dural aluminum or monel metal (as opposed to leather or rubber) until the bones are developed sufficiently to allow subtalar (triple) arthrodesis to be performed in order to avoid the symptoms of flat feet in adult life.

Cavus foot. This condition consists of an excessively high longitudinal arch due to overactive long toe extensor tendons which produce hyperextension of the metatarsophalangeal joints, hyperflexion of the interphalangeal joints, and depression of the metatarsal heads (Fig. 6). Such findings should cause the examiner to think in terms of heredity, short shoes, poliomyelitis, congenital lues, or neurological conditions affecting the posterior and lateral columns of the spinal cord. Metatarsal pads, metatarsal bars, and stretching exercises are useful in the early conservative treatment. Later, transplantation of the long toe extensor tendons is indicated; and if in addition, bony deformity is present subtalar arthrodesis must be added.

Fig. 2. Weak feet. Note on the left that longitudinal arches are relaxed, and on the right patient is attempting to elevate the arches but is unable to do so completely. Compare with Figure 1.

Koehler's disease. This condition is an osteochondritis or inflammatory reaction resulting in flattening, condensation, and irregularity of the tarsal navicular (scaphoid) bone due to aseptic necrosis (Fig. 7). It occurs in children between 5 and 10 years of age. The symptoms consist of pain upon walking and tenderness over the navicular bone, often associated with redness and swelling. The diagnosis is confirmed by the x-ray. Treatment consists of hot epsom salt soaks and massage for the pain and swelling, and a monel metal or aluminum arch made from a plaster mold to fit and to support the foot. Inactivity, immobilization, and plaster casts are not necessary, and complete spontaneous recovery is the rule.

Freiberg's disease. This is another member of the family of osteochondroses which affect the feet of children (2). It is a progressive flattening of a metatarsal head, generally the second or third, due to a circulatory disturbance producing aseptic necrosis with fibrous tissue replacing the bone tissue (Fig. 8). Gradually the metatarsal head develops a flat and deformed contour with increased calcification, a projecting bony rim, and frequently, loose bodies. The early symptoms are pain, swelling, and redness; and the late symptoms are those of metatarsalgia or pain in the metatarsal area of the foot. Examination early reveals tenderness and swelling localized to a metatarsal head and later, a palpable bony rim extending around the head and associated

Fig. 3. Talipes calcaneovalgus. Note that the excessive dorsiflexion allows the dorsum of the feet to reach the tibiae.

Fig. 4. Talipes calcaneovalgus. Note in same feet as Figure 3 that eversion and excessive relaxation of longitudinal arches produce valgus and pronation of the feet.

Fig. 5.

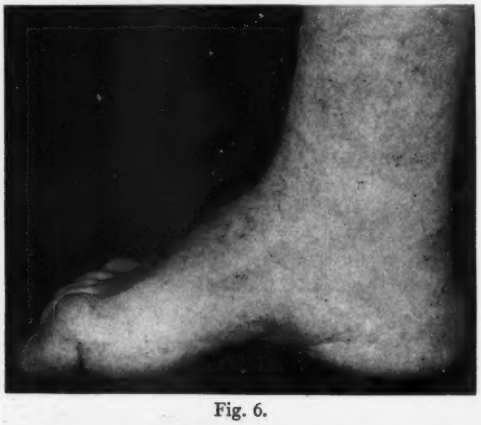

Fig. 6.

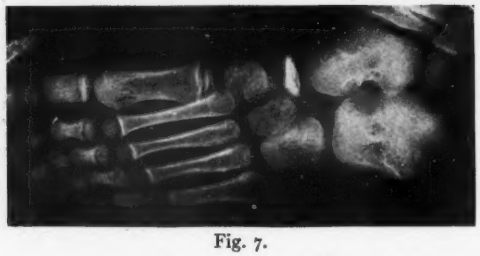

Fig. 7.

Fig. 5. Plantar flexed talus. Note that talus deviates excessively toward a sole of the foot producing the rocker deformity.

Fig. 6. Cavus foot. Note high longitudinal arch, hyperextension of metatarsophalangeal joints, and hyperflexion of interphalangeal joints.

Fig. 7. Koehler's disease. Note in this roentgenogram the flattening, the condensation, and the irregularity of the navicular bone.

Fig. 8.

Fig. 9.

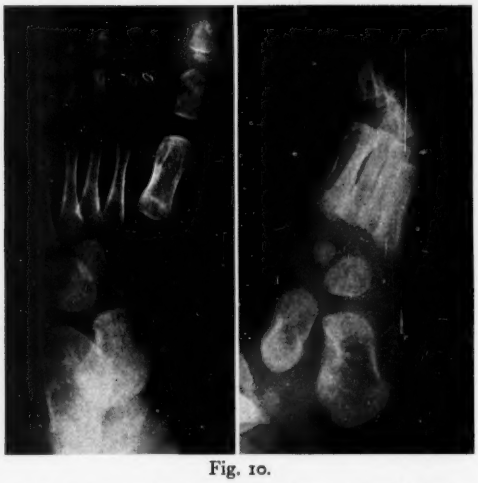

Fig. 10.

Fig. 8. Freiberg's disease. Note flattening, calcification, bony rim, and loose body at third metatarsal head on right.

Fig. 9. Calcaneal apophysitis. Note soft tissue swelling and irregularity at calcaneal epiphysis, which is difficult to see in reproduced roentgenogram.

Fig. 10. Fracture of foot (2 cases). Note on the left a transverse fracture of proximal phalanx of first toe in a child aged 2 years, and on the right a fracture of the base of the first metatarsal bone in a child aged 21 months.

with slight shortness of the toe. Early treatment should consist of hot epsom salt soaks, massage, and a metatarsal pad or metatarsal bar applied to the shoe or to an insole. Again, immobilization is not necessary for it has been shown to have no effect on the progress of the

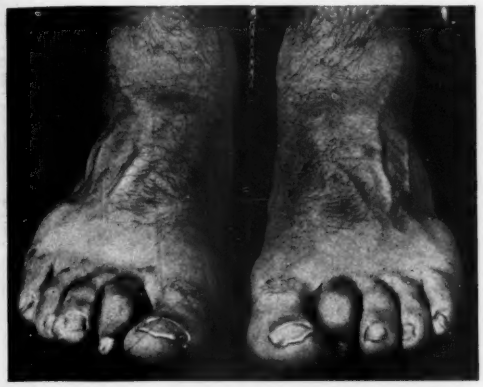

Fig. 11. Hammer toes. Note flexion deformity at proximal interphalangeal joint of each second toe.

disease. Later, surgery may be necessary in the form of excision of the bony rim of the metatarsal head; or removal of loose bodies from the joint; or in some cases resection of the head of the metatarsal bone.

Calcaneal apophysitis. This is an osteochondritis of the calcaneal tubercle and belongs to the group of osteochondroses (Fig. 9). The symptom is that of pain at the insertion of the calcaneal tendon. The examination reveals an enlarged mildly tender, calcaneal tubercle. Treatment consists of hot epsom salt soaks and massage to relieve the pain and tenderness at the tubercle; and elevation of the heel of the shoe to relieve the pull of the calcaneal tendon at its insertion. Immobilization and inactivity rarely are necessary. The prognosis is good.

Fracture. Fractures of the feet in children are considered rare because of the excessive flexibility and cartilaginous elasticity of the feet in youth. This assumption, however, often leads to delayed or mistaken diagnoses. Two such examples are demonstrated in Figure 10 which shows on the left a transverse fracture of the proximal phalanx of the first toe in a child 2 years of age who caught his foot in his pajamas while running; and on the right a fracture of the base of the first metatarsal bone, with the proximal fragment displaced dorsally, in a child 21 months of age who dropped a 30 pound pump on his foot. These two children were seen within 10 days

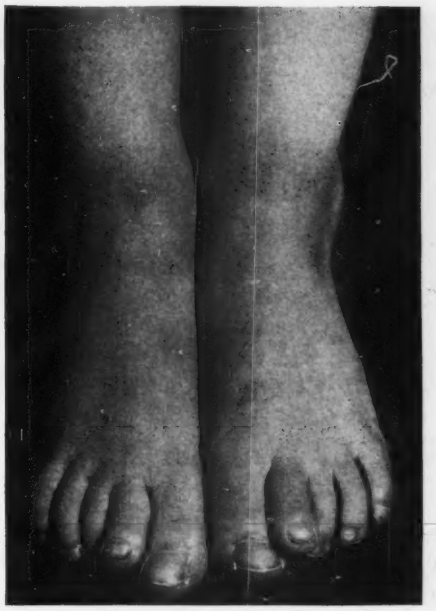

Fig. 12. Overlapping toes. Note that each second toe is elevated above the adjacent toes.

Fig. 13. Hallux varus. Note medial deviation of first toe on the right while the opposite foot is normal.

of each other showing that such fractures are not uncommon; and because of the severe swelling, pain, increased heat, and redness one had been treated for 3 days for "acute infection," showing that a correct diagnosis of such fractures often is delayed. These statements are not made in criticism but to emphasize the point that fractures of the feet even

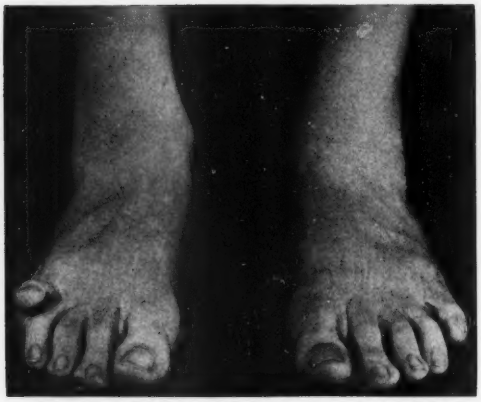

Fig. 14. Subluxated fifth toe. Note that fifth toe on the left is displaced dorsally and adducted over the fourth toe while the opposite foot is normal.

Fig. 15. Varus toes. Note that the distal phalanx of each oft he lateral three toes is curved under the inner adjacent toe.

in very young children should be kept in mind to prevent delayed diagnosis and treatment.

Hammer toe. The term applies to a flexion deformity of either or both of the interphalangeal joints of any toe, generally the second (Fig. 11). The condition is a congenital defect which bears no relation to footwear except that short shoes are a possible cause when the second toe is longer than the first. The complaint generally is of a cosmetic nature on the part of the parent although later a dorsal callosity may develop and become painful to the patient. Splints of all types and stretching of the deformity are of no value from a curative standpoint. After about 10 years of age arthrodesis of the affected joint may be performed for permanent correction and relief.

Overlapping toe. This is a congenital defect in which a toe is elevated above the adjacent toes, most often the second (Fig. 12). Splints to hold the toe in position or the strapping of the toe to an adjacent toe may be used but will not correct the condition. Often the elevated toe will assume a normal position without treatment but if the condition persists and becomes symptomatic later in life, amputation may become necessary.

Hallux varus. This term is applied to abduction or medial deviation of the first toe (Fig. 13). Although congenital, it is more or less a normal finding in infants. It produces no symptoms and does not require treatment because as soon as shoes are worn the toe will assume a straight position.

Fig. 16. Webbed toes. Note that web of second and third toes of each foot extends on the right to the proximal interphalangeal joints, and on the left to the distal interphalangeal joints.

Subluxated fifth toe. The condition is a congenital deformity in which the fifth toe is subluxated dorsally, rotated externally, and adducted over the fourth toe (Fig. 14). In the past, surgery consisted of the amputation of the toe but today the treatment of choice is to remove the contracture and to straighten the toe by the Lantzounis procedure (5).

Varus toe. This is another congenital deformity in which the distal phalanx of one or more of the lateral four toes is curved over or under the inner adjacent toe (Fig. 15). Often the deformity is painful, due to weight bearing on the bottom toe or rubbing of the shoe on the top toe. Generally the deformity is fixed, preventing the use of conservative methods of treatment. Correction is obtained by arthrodesing the involved interphalangeal joint with the phalanx in straight alignment.

Web toe. This condition is a congenital defect in which segmental differentiation of the toes fails to take place. The webbing may be by skin and soft tissue or by bone. The web may extend only to the proximal interphalangeal joints, as seen at the second and third toes on the right in Figure 16; or to the distal interphalangeal joints as seen on the left in the same figure; or to the tip of the toes (Fig. 17). Generally speaking, the digits are distinct with the bones, joints, and nails developed normally. Inasmuch as symptoms rarely develop in such toes, treatment is unnecessary except occasionally when plastic repair is performed for cosmetic reasons.

Fig. 17. Webbed toes. Note on the left that web extends to the tips of the second and third toes which the roentgenogram on the right demonstrates to be due to soft tissue only.

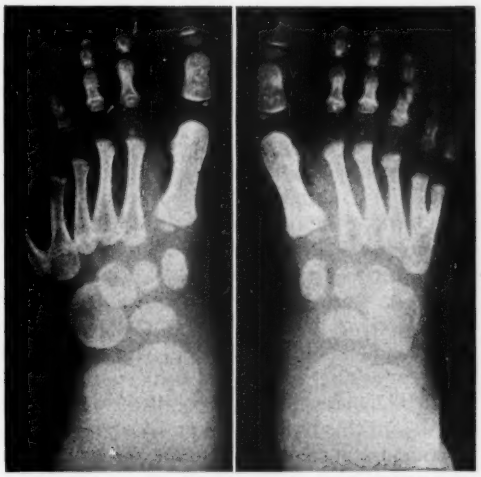

Fig. 18. Accessory toes. Note on the right that the six toes appear normal and surgery is not indicated, while on the left the last toe is prominent and surgery is indicated.

Fig. 19. Accessory toe. Note on the left in this roentgenogram the projecting segment of bone which requires excision.

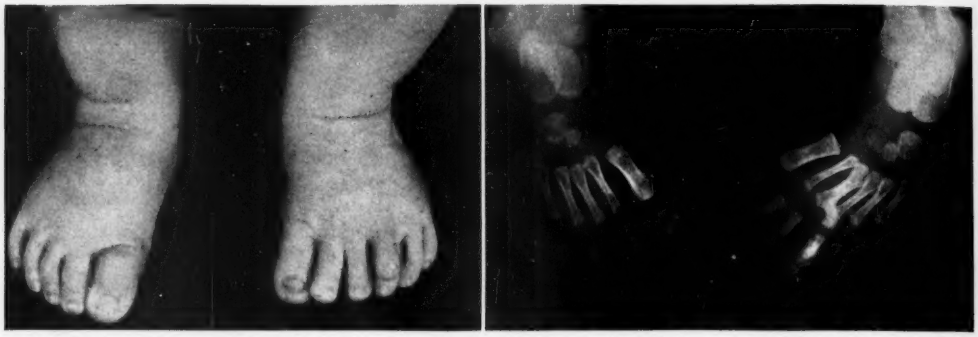

Fig. 20. Accessory toes. Note that because one of the seven toes on the left foot overlies the fourth toe, surgery is indicated.

Accessory toe. Not infrequently children are born with extra toes and whenever the x-ray studies reveal all digits to be normal no treatment is indicated, as in the foot on the right in Figure 18. However, at times the abnormal position of the extra toe, as seen on the left in the same figure, or the projecting segment of bone (Fig. 19) produce a deformity which is unsightly or symptomatic due to shoe pressure. In fact, Figure 20 shows the foot on the right to have seven toes, one of which overlies the fourth toe and needs to be removed. The only treatment is amputation of the supernumerary digit, preferably at birth.

Callosities. So called corns develop in children only on the toes, most frequently the first and the fifth. The condition is a mere protective thickening of the skin due to abnormal shoe pressure. It produces no symptoms but the mother notices the skin to be red and thickened. Such a case is demonstrated in Figure 21 where for photographic reasons chalk was applied to the reddened areas of each fifth toe to show their size. It is an indication of improper fitting of the shoes, either too short or too narrow, and is relieved completely by obtaining larger shoes.

Fig. 21. Callosities. Note that chalk has been applied to the callosities of each fifth toe to show their size.

Diaphoresis. Mothers frequently complain that their children show excessive perspiration of the feet. In general, this is a normal manifestation of the great activity and high metabolism which children have. However, when treatment is indicated the following prescription is of value:

	Grams
Acidi salicyli	3
Acidi borici	10
Talci qs	100

The powder should be applied each morning and each night to the feet, with particular attention to the moist areas between the toes. In addition, the powder should be dusted into the shoes at night to absorb the moisture and to produce a thin protective film if the shoes are to be worn the following morning.

Metatarsus varus. The common name for this condition is pigeon toe. It consists of varus or adduction of the forefoot on the rearfoot. The deformity may be postural or structural, and this differentiation is extremely important because of the difference in treatment and prognosis.

In the postural type, examination will reveal the deformity to be flexible, and to be

Fig. 22. Metatarsus varus (postural). Note on the left that the forefoot is curved inward while the opposite forefoot is normal.

Fig. 23. Metatarsus varus (postural). Note in same feet as Figure 22 that with light pressure the forefoot on the left is as straight as the normal one on the right.

overcorrected easily by passive manipulation. In Figure 22 the forefoot on the left is curved inward and presents a varus deformity but Figure 23 demonstrates that with light pressure the same foot is as straight as the normal one on the right. Although such medial deviation of the forefoot is not uncommon in infants, internal tibial torsion and internal rotation of the entire extremity must be ruled out. The treatment consists only of applying a wedge to the outer aspect of the sole of the shoe, measuring 1/8 inch in young children and 3/16 inch in older children. Upon walking such wedges automatically force the forefoot outward into a straight position and the correction gradually becomes permanent.

In the structural type, examination will reveal the deformity to be fixed, and overcorrection by passive manipulation not to be possible (Fig. 24). This type of deformity belongs to the clubfoot family, requires much more extensive and involved treatment, and the prognosis for full correction is much less favorable. Treatment should consist of wedging plaster casts in which the forefoot is forced gradually into a position of overcorrection and held there for 6 weeks.

Talipes equinovarus. This is the medical term for true clubfoot, and the colloquial term "clubfoot" should be reserved for this type of deformity only. It is an inherited and congenital deformity of a severe type (Fig. 25). The prognosis for cure always must be guarded. The diagnosis is established by the possible history of similar deformities in other members of the family and the physical findings of a fixed deformity in which the forefoot is turned in, the heel drawn up, and the foot held in inversion and plantar flexion. In those cases in which the examination is difficult because the degree of deformity is mild, a simple method of establishing the diagnosis is to pal-

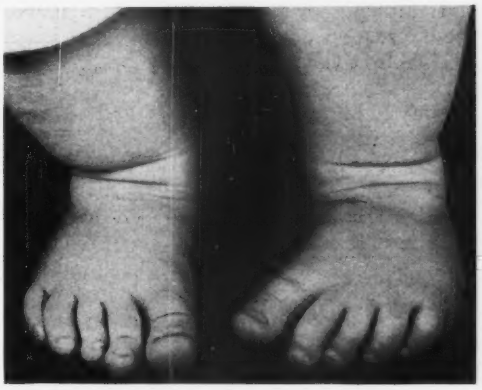

Fig. 24. Metatarsus varus (structural). Note medial deviation and excessive adduction of forefoot on the right.

Fig. 25. Talipes equinovarus. Note that in this infant there is a true clubfoot on the left and a normal foot on the right.

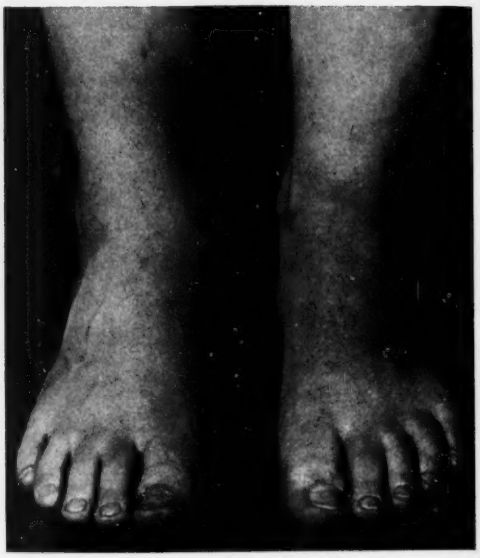

Fig. 26. Normal feet. Note good longitudinal arches, straight forefeet, well spaced toes, and proper alignment of feet on the legs.

pate the space between the navicular tubercle and the medial malleolus to note the width of the space and whether the two bones are approximated (6). The treatment of clubfeet is tedious, difficult, and highly technical. It should be instituted at birth, even while the baby still is in the hospital, because the ease and degree of correction is related closely to the age of the patient. Although many types of treatment have been and are being used, the most dependable and best established method for correction is to apply and to wedge plaster casts after the method of Kite (3). Surgery today is reserved for residual deformities later in life.

Normal feet. So much has been stated about abnormal feet that it seems appropriate to mention the subject of normal feet. In Figure 26 it is noted that a normal foot presents a good longitudinal arch without the presence of pronation. The forefoot is well aligned on the rearfoot and the toes are well spaced, straight, and lie flat. The ankles do not bulge internally or externally, and the foot as a whole is straight forward and properly aligned on the leg.

Shoes. The term "orthopedic shoe" should be discarded because it implies that a shoe has been specially constructed for the child's foot. From the foregoing comments it is evident that no single pair of shoes can be correctly constructed to take care of all of the defects which children may show. It implies further that the manufacturer is treating a patient who has never been seen. In such instances, the manufacturer builds into the shoes all the appliances known to the orthopedist, in a more or less "shotgun prescription" to cover all the conditions which might exist. In consequence, the patient may be damaged by certain appliances while being aided by other corrections. Figure 27 shows on the left a pair of orthopedic shoes with built-in appliances and swung-in toes while on the right is a pair of normal shoes which are considered proper for children. The latter shoes are of the blucher type which lace across a tongue, and are well made of solid leather with thick, inflexible soles. In general, they should be oxfords inasmuch as high shoes offer no additional support and are of no value except for protection against the elements. Booties, artificial leather,

Fig. 27.

Fig. 28.

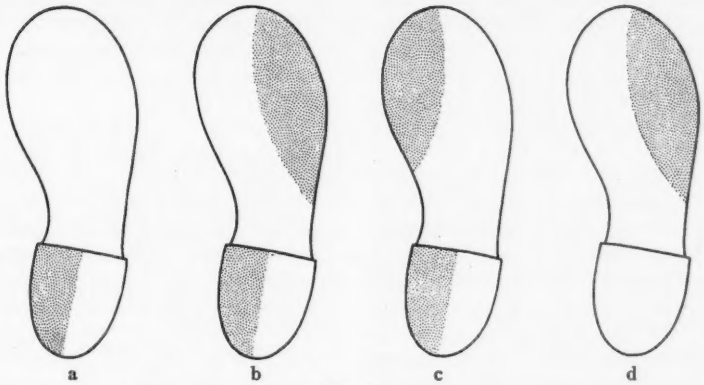

Fig. 29.

Fig. 27. Shoes. Note so called orthopedic shoes on the left compared to normal shoes on the right.

Fig. 28. Shoes. Note shoes with swung-in toes on the left, which produced callosities on fifth toes of normal feet in the center, relieved by straight shoes on the right.

Fig. 29. Shoe wedges. Note proper position for, a, inner heel wedge; b, inner heel and outer sole wedges; c, inner heel and inner sole wedges; and, d, outer sole wedge.

rubber sole and soft sole shoes never should be used. With proper shoes the desired corrections may be obtained by first diagnosing the patient's condition, and then ordering by prescription the appliances which are indicated. In this way the patient receives specific treatment for the specific defect. Figure 28 is a typical example of the unfortunate use of so called orthopedic shoes. In this particular instance the feet were entirely normal, as can be seen in the center, but a standard make of orthopedic shoes was prescribed for the patient. The swung-in toes of the shoes on the left obviously could not fit the straight normal feet of the child. The result was thick callosities on the lateral aspect of each fifth toe, which by close examination can be seen. Following the removal of the orthopedic shoes, and the substitution of the straight normal shoes on the right, the callosities disappeared rapidly and the patient's complaints ceased.

Shoe wedges. Much confusion exists as to the manner in which shoes should be wedged for purposes of correction of the various deformities of the feet. Wedges are of value only when applied to solid leather shoes with thick soles. They should be placed outside and not inside the shoes, and should be inserted between the soles and within the substance of the heels so that they are not subject to wear and tear. Their thickness is thus maintained and after being properly and accurately placed by an orthopedic shoemaker, the shoes may be half soled and the heels may be built up by an ordinary shoe repair shop. The wedges should vary in width from 1/8 to 3/16 inch depending upon the age of the child and the degree of deformity.

Figure 29 demonstrates the common types of wedges. a, Represents an inner heel wedge which is used for pronated feet; b, demonstrates inner heel and outer sole wedges which are used for weak feet; c, represents inner heel and inner sole wedges which are necessary for severe relaxation of the longitudinal arches in talipes calcaneovalgus (Inasmuch as almost all shoes for children up to the age of 6 years, or size 12, are made without heels the wedge may be placed throughout the medial border of the shoe); d, demonstrates an outer sole wedge which is used for the postural type of metatarsus varus.

Shoe-fitting fluoroscopes. Mention should be made of the danger which is inherent in the use of the fluoroscope, by certain retail stores, in the fitting of children's shoes (1). The hazards consist of uncontrolled length of exposures as the mother travels from store to store, continues to fit shoes after shoes, plus the mere curiosity on the part of the customer. To date injuries have not been reported but this does not imply that skin damage or epiphysial distortion may not have occurred, because sufficient time may not have elapsed for such injuries to become apparent or because such injuries may have occurred and been attributed to other causes. Shoes always have been and may still be fitted by the ordinary methods of measurement and observation, particularly when there is nothing more to do than to have the shoe one thumb-breath longer and one little finger-width wider than the foot. It appears that fluoroscopy for shoe fitting may be employed more on an advertising basis than on a scientific basis.

SUMMARY

1. Brief comments are presented concerning each of the ordinary foot problems in children.

2. The various conditions are discussed from a practical standpoint with reference only to diagnosis and treatment.

3. Proper shoes, wedges, and fitting are described in detail.

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EXPERIMENTAL HEPATIC-PORTAL ARTERIOVENOUS ANASTOMOSES

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THE important role of the liver in normal and pathological physiology is well recognized. Its circulation has long been an intriguing problem in health and disease. The following is a report of the successful transplantation of the hepatic artery into the portal vein of dogs. This unique type of arteriovenous fistula is well tolerated by dogs up to periods of at least 18 months and may afford a method of altering and increasing the oxygenated blood supply of the liver. It has permitted the uneventful survival of dogs after ligation of their hepatic artery and its branches.

Several postmortem anatomical and perfusion studies of the circulation of the liver have been made in past decades (13, 20, 6). The results have been contradictory and subject to criticism because of the abnormal conditions of the liver and the types of perfusates. In general they have indicated an increased resistance in the portal circulation in the cirrhotic liver. Numerous intrahepatic arteriovenous shunts were present in normal and abnormal livers. Dock (7) has concluded that there may be a reciprocal relationship between hepatic arterial and portal venous blood flow that is proportional to the degree of arterial pressure and intrahepatic resistance. These relationships may be altered by the increase in arteriovenous shunts within the liver that seem to occur in cirrhosis. Wakim and Mann (26, 27) by use of the quartz rod transillumination technique and direct visualization of the hepatic circulation in the frog and rat have made some interesting observations. They described an intermittent rhythmicity of the hepatic circulation and about 75 per cent of the liver was inactive under ordinary conditions. They noted great functional reserve in vascular activity with many interlobar and intrahepatic arteriovenous shunts.

Grindlay and his associates, by use of the thermostromuhr, were able to measure the portal and hepatic blood flow of the liver in dogs. They found an average flow of 100 cubic centimeters per 100 grams of liver per minute. The hepatic artery contributed 10 to 30 per cent of this total in nonanesthetized animals. During anesthesia, hepatic arterial flow was greatly increased and even exceeded portal flow in 2 instances. Inflow and outflow varied in such a fashion as to indicate a storing and then expulsion of blood from the liver. This may be due to the action of a peculiar muscular sphincter-like mechanism at the outlet of the hepatic vein of the dog described by Bauer and his associates.

The importance of oxygen to the liver in shock has recently been reviewed by Hoff (15, 16). Goldschmidt (10) and Ravdin (24) have indicated that certain toxic effects of chloroform anesthesia may be reduced when the chloroform is volatilized with oxygen instead of air. The interesting experiments of Frank and his associates indicate that irreversible shock by bleeding in control animals was prevented in a second series by cross transfusion of arterial blood directly into the splenic veins of the shocked animals. In a third series of animals, similar direct transfusion into the jugular veins of shocked dogs was without effect. Shorr and his associates in a series of experiments have postulated a vasodepressor substance elaborated by the liver in shock, possibly in response to anoxemia.

Bradley (3, 4) in ingenious experiments has estimated the variations in hepatic blood flow in man during health and disease. By catheterizing the hepatic veins and utilizing a modified Fick principle he has estimated the

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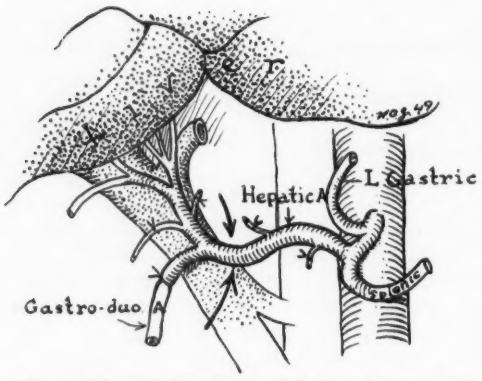

Fig. 1. Schematic illustration of the hepatic artery and its variable branches in the dog.

blood flow through the liver on the basis of the absorption of bromsulfalein. His estimates of normal blood flow were similar to those of Grindlay, namely, 1 cubic centimeter per gram of liver per minute. Exercise and the erect posture caused a marked decrease in hepatic blood flow. A pyrogenic reaction caused a marked increase in blood flow. A marked reduction in blood flow was noted in cirrhotics with an increase in the difference of the arterial and hepatic venous oxygen saturations. The therapeutic implications of physical rest and higher oxygen saturations of portal blood are suggested from these experiments in certain toxic and inflammatory liver diseases.

Numerous reports have appeared concerning the fatal effects of ligation of the hepatic artery in man (11), and experimentally in the dog (17). Narath attempted to implant the hepatic artery or the renal artery into the portal vein in 1916 in an effort to circumvent experimentally the fatal results of hepatic artery ligation. He used various methods of anastomosis; namely, end to side, open side to side, closed suture method of side to side, and implantation of the artery into the vein in a method identical to that described by Hodge and Bridges. In some animals the arteriovenous anastomoses appeared to be life saving though later thrombosis occurred in all but 2 animals. Naegeli anastomosed the hepatic artery in the dog end to end with the superior mesenteric vein over a splinting metal tube with questionable success in 1 instance. Ghiron and Badalla have anastomosed the hepatic artery end to end with the splenic vein and had patent anastomoses demonstrated at postmortem examination. The studies of their animals were incomplete but apparently they survived in some instances with normal liver function which the investigators attributed to the influence of the spleen. Markowitz (18) anastomosed the aorta to the portal vein but his animals died with congestive liver necrosis. In a more recent report, Markowitz (19) attempted end to side anastomoses of the hepatic artery into the portal vein. Though his dogs survived, he found that all the anastomoses had thrombosed. In all of his controls with simple ligation of the hepatic artery, death occurred in 100 per cent of the animals. In a third series of animals with simple hepatic artery ligation massive doses of penicillin were administered with survival of almost all animals. His conclusions from this work are that the antibiotics reduce the gas bacillus infection that inevitably follows liver necrosis in a dog, allowing survival. The hepatic artery's immediate function under these circumstances is to furnish sufficiently high oxygen tensions to prevent proliferation of the anaerobes. Davis and associates have also had similar results.

In summary, ligation of the hepatic artery with preservation of its collateral or a major branch does not usually cause death in man or the experimental animal. Ligation of all major branches and collateral is almost invariably followed by death unless the animal is protected from infection by the antibiotics. Attempts have been made to arterialize the portal vein, but to date, none have been completely successful as far as we know.

EXPERIMENTAL METHODS

A new method of producing an hepatic-portal arteriovenous fistula was devised. Because of the small lumen of the hepatic artery and its relative inaccessibility, all classic end to side anastomoses with interrupted No. 00000 silk sutures thrombosed. Accordingly, after carefully freeing the hepatic artery from its surrounding autonomic nerve plexus and individually ligating and dividing each of its branches, which were variable, the vessel was

implanted into the portal vein as indicated in Figures 1 and 2. A specially devised clamp, used in the open method of Eck fistulas by Dr. G. H. Whipple, was utilized to control bleeding from the portal vein. A Blalock clamp controlled the hepatic artery. No sutures were placed into the intima of the artery, and after loosely closing the vein about the hepatic artery, only one anchoring stitch into the adventitia was necessary to prevent the artery from retracting. A long subcostal incision or a T rectus incision with a sandbag under the dog's back provided excellent exposure. The hepatic artery, though easily palpable laterally, was exposed through the lesser omental bursa. It was necessary carefully to dissect away the large lymph node that lies on the portal vein medially to secure adequate exposure of the vein. Care should be taken not to angulate the artery in its implantation, so that its effective pressure is not reduced. Also, the artery should point toward the liver to prevent possible eddies in the portal vein that might cause a thrombosis. Not more than 4 millimeters of the artery and no suture material should project into the portal vein for similar reasons. As in all vascular surgery, meticulous gentle sharp dissection and absence of tension are imperative. This method is somewhat similar in principle to that employed by Hodge and Bridges for implantation of the thoracic duct into the azygos vein except that no suture material is introduced into the lumen of the vein. Upon completion of the procedure after opening the clamps, a thrill should be readily palpable at the anastomotic site. Bleeding was usually minimal. Pulsation of bright red arterial blood was seen through the blue thin-walled portal vein. If pulsations were not visible and a thrill was not palpable, the anastomosis was usually unsatisfactory as the full effective pressure and blood flow of the artery was not being delivered into the vein. Serosanguineous fluid, blood, or clots were gently removed from the area and the abdominal wound was closed with interrupted silk sutures. The animals were returned to routine care. No antibiotics or anticoagulants were employed. All operations were performed with sterile technique and intravenous nembutal anesthesia.

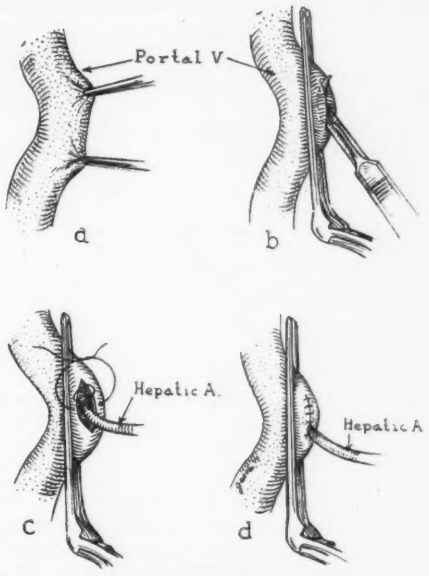

Fig. 2. Schematic illustration of the steps in the formation of the hepatic-portal arteriovenous fistula.

After a month the animals were re-explored to assure patency of the anastomosis. At these times the mesentery was observed carefully for congestion, the livers were biopsied and venous pressure and oxygen saturation studies were carried out. Three animals were subjected to chloroform anesthesia. Three animals were subjected to double depletion studies as the best experimental index of liver function. The animals in such studies were placed on a very low protein diet and biweekly bleeding after the method of Whipple and Robbins. The composition of this diet is presented in Table I. Thirty grams of horse meat were added each day and mixed with 250 grams of this diet to increase its palatability, obviating the necessity of spoon feeding if refused by the animals. The diet contained approximately 514 calories per 100 grams and a nitrogen content of 0.012 per cent. Nitrogen balances were calculated and recorded. At the end of a suitable period, determined by the low level of protein and hemoglobin values, the animals were placed on a high protein and iron diet and bleeding was discontinued. This diet contained 250 grams of horse meat and

TABLE I.—COMPOSITION OF VERY LOW PROTEIN DIET

	Grams
Sucrose (cane sugar)	2,600
Bone ash	78
*Salt mixture	78
Potassium phosphate (KH_2PO_4)	310.0 grams
Sodium chloride	105.0
Potassium chloride	120.0
Calcium phosphate	149.0
Calcium carbonate	210.0
Magnesium sulfate (anhydrous)	90.0
Ferric phosphate ($FePO_4 \cdot 4H_2O$)	14.7
Manganese sulfate (anhydrous)	.2
Alum ($K_2Al_2(SO_4)_4 \cdot 24H_2O$)	.09
Copper sulfate ($CuSO_4 \cdot 5H_2O$)	.39
Sodium fluoride	.57
Potassium iodide	.05
Liver powder	26
Powdered yeast (Type 200-B)	26
Mazola oil	235
Cod liver oil	50
Lard melted	490

*(Science, 1932, 75: 339)

50 grams of the low protein diet each day. The rate of weight gain, increase in plasma protein levels, increase in hemoglobin and hematocrit served as an excellent index of liver function. Venous pressures in the portal system and caval systems were measured in dogs by direct manometric readings and by recordings on photographic film in conjunction with the electrocardiograph and respiratory exchange by methods of Bembower, Schilling, Hoffman, and Brown. The animals have been carefully observed clinically for periods up to 18 months. A control series of 10 dogs was operated on with ligation of the hepatic artery and its collateral branches without implantation into the portal vein.

RESULTS

A series of 11 dogs was used to establish the technique of the operation and to secure animals for observation and study. The results of those operations are tabulated in Table II. Three deaths occurred from hemorrhage, portal thrombosis, and acute pancreatitis respectively. Four animals developed thrombosis of their hepatic arteries at varying periods after the operation from fibrosis and kinking. This process was slow enough to allow development of adequate arterial collateral and survival. Four animals have had patent fistulas. The first died after exploration following chloroform anesthesia. It is assumed that

TABLE II.—TRANSPLANTATION OF HEPATIC ARTERY INTO PORTAL VEIN AFTER LIGATION OF BRANCHES

No.	Fate	Remarks
48–3	Survived	Thrombosed—3 months
47–240	Survived	Thrombosed—1 month
48–200	Died (½ d.)	Artery retracted—hemorrhage
48–10	Died (1 d.)	Portal thrombosis
48–90	Survived	Splenic artery used—thrombosed—5 months
48–182	Survived	Thrombosed—3 months artery kinked
49–40	Died (1 d.)	Acute pancreatitis patent artery
47–183	Survived	Studied metabolically
48–65	Survived	Studied metabolically
48–150	Survived	Studied metabolically
48–223	Survived	Studied metabolically

the intravenous nembutal superimposed on a moderately damaged chloroform liver was too great a strain for the dog. The remaining 3 animals have survived uneventfully for periods up to 18 months and will be described in detail.

48–65. A 30 pound young mongrel female was operated on May 19, 1948. An arteriovenous fistula was performed as described previously with ligation of the hepatic artery and its branches near the liver. Recovery from anesthesia was quite prompt and the dog was placed on routine care. On July 19, 1948, a chloroform anesthesia was induced of 1 hour's duration after 3 days of fasting. No discernible clinical effect was noted from these anesthesias and the animal survived uneventfully. On November 27, 1948, the animal was re-explored. There was no congestion of the mesentery. The liver appeared pinker than normal. This observation was carefully confirmed by qualified observers. There was a marked coarse thrill at the site of the arteriovenous anastomosis. The liver was biopsied and microscopically appeared normal. On March 11, 1949, the animal was placed in a metabolism cage and double depletion of his protein stores was carried out as outlined. The results of this experiment are tabulated in Figure 3. The prompt response to a high protein diet and cessation of bleeding indicated a normal liver function. On October 4, 1949, the animal was again re-explored. There were no adhesions; the liver was pinker than normal; and there was no mesenteric congestion. At the site of the anastomosis and proximal toward the liver there was dilation of the portal vein two times its normal diameter with some thickening of its wall. There was a continuous thrill but of lesser intensity than originally, presumably because of the dilation of the portal vein. Direct manometer pressure studies in the

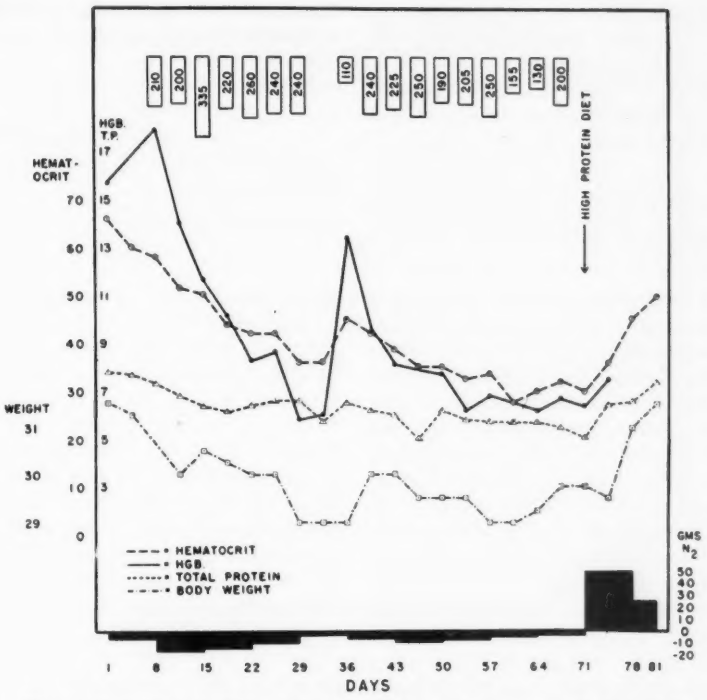

Fig. 3. Illustration of effects of double depletion and recovery on the hemoglobin, hematocrit, total protein, body weight, and nitrogen balance of dog 48–65 one year after formation of hepatic-portal arteriovenous fistula.

portal system revealed a maximum pressure of 14.8 centimeters of water at the site of the anastomosis. Oxygen saturation of the portal blood as it entered the liver was 60.1 per cent compared with 48.2 per cent in the vena cava and 69.2 per cent in the aorta. Other control studies have indicated relatively identical oxygen saturation values in the vena cava and portal vein. The low values here are all assumed to be due to the low arterial saturation because of the nembutal anesthesia, and the prolonged supine position of the dog. An arterial sample from the femoral artery before anesthesia revealed an oxygen saturation of 96.2 per cent. Biopsy of the liver was normal microscopically at this time. The animal again recovered uneventfully and continues with routine care and regular observation.

48–150. A 40 pound male sheep dog was operated on January 18, 1949, and a hepatic-portal arteriovenous fistula was performed with ligation of the branches of the hepatic artery. Recovery was prompt and uneventful. The dog was explored on March 22, 1949, and the liver appeared pinker than normal. A biopsy revealed a normal liver microscopically. There was no congestion of the mesentery. A marked thrill was palpable at the site of anastomosis. Venous pressures were recorded as described previously. The highest pressure in the portal system was 16.5 centimeters of water at the height of inspiration at the site of the anastomosis. This is shown in Figure 4. The pressures are very similar to a control animal and vary with heart beat and respiration in a predictable manner. On April 20, 1949, the animal was placed in a metabolism cage and doubly depleted with a prompt response after cessation of bleeding and the addition of a high protein diet in a manner similar to that for dog 48–65 illustrated in Figure 3. This animal is being maintained for long period of observation.

48–223. A 40 pound male was operated on May 24, 1949, and a hepatic-portal arteriovenous fistula was performed with ligation of the branches of the hepatic artery. Recovery was prompt. The animal was explored July 28, 1949, and a marked thrill was palpable at the anastomosis. The liver was pink. There was no congestion of the mesentery. Portal pressure measured 20 centimeters of water in this animal. The animal was placed in a metabolism cage on September 19, 1949, and double depletion begun. The data from this experiment are summarized in Table III.

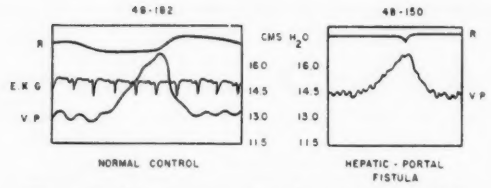

Fig. 4. Portal venous pressure of a normal control dog and an animal with a hepatic-portal arteriovenous fistula. Note effect of respirations and heart beat on the venous pressures of both animals.

TABLE III.—SUMMARY OF EFFECTS OF DOUBLE DEPLETION AND RECOVERY ON DOG 48–150

	Total protein milligrams per cent	Hemoglobin milligrams per cent	Hematocrit per cent	Weight pounds
Control	7.5	12.6	49	30
1 month depletion	5.7	7.9	41	37
1 week recovery	7.3	9.5	44	38

The second series of dogs with ligation and division of the hepatic artery and its branches without implantation into the portal vein is summarized in Table IV. All dogs except 2 died promptly with liver necrosis and varying degrees of gas infection. It is assumed that the 2 animals that survived had an unobserved collateral vessel or aberrant artery that allowed sufficient arterial blood to the liver. One of these animals died promptly after an Eck fistula with massive necrosis of the liver, indicating the tenuous nature of this collateral. Another animal not reported in this series had an Eck fistula performed with uneventful recovery. A month later the branches of the hepatic artery were ligated and the artery was wrapped with unsterilized cellophane. This material had previously caused marked fibrosis in independent experiments by Dr. H. E. Pearse. The animal survived uneventfully and was sacrificed 2 months later. Red liquid latex was injected prior to postmortem dissection. The hepatic artery was completely occluded but sufficient collateral was found in the diaphragm and particularly along the layers of fibrosis and granulation about the cellophane to prevent liver necrosis, despite complete diversion of the portal blood flow into the vena cava and occlusion of the hepatic artery and its branches.

DISCUSSION

The purpose of this investigation to date has been the development of a successful method of arterializing the portal vein and the observation of these animals for a sufficiently long period to determine the early and intermediate tolerance of this procedure. Though large numbers of animals have not been used, this type of arteriovenous anastomosis can be simply performed and to our knowledge is the first completely successful approach to this problem to date. During the past decades tremendous significance has been attached to the protein concentration of the blood going to the liver for synthesis and utilization. Experimental evidence from several sources has been cited indicating the importance of the circulation of the liver. These papers have directly or indirectly stressed the importance of oxygen saturation of the blood reaching the liver by its dual source. This method reported may make possible the study of liver function with increased arterial blood supply and oxygen. Before any clinical approach to the problem may be made, it is imperative that the effects of such an arteriovenous fistula be observed experimentally over a sufficient period and the factors of a pathological liver and its circulation be evaluated before superimposition of an abnormal vascular shunt.

Some of the observations which have been made deserve emphasis. An arteriovenous anastomosis into the portal vein will protect the animal from death from ligation of the hepatic artery and its branches. Even if a later thrombosis occurs, collateral circulation has had an opportunity to develop, and the animal is spared. Actually on the basis of our unpublished observations, it is practically impossible to produce liver damage by slowly removing the various portions of the liver's circulation because of the development of this collateral. In the intermediate period following these anastomoses there seems to be no clinically noticeable ill effect in the dog. No significant elevation of venous pressure, no congestion of the mesentery, and no apparent cardiovascular embarrassment has been ob-

TABLE IV.—LIGATION OF HEPATIC ARTERY AND BRANCHES WITHOUT TRANSPLANTATION INTO PORTAL VEIN

No.	Fate	Remarks
48–171	Died—6 days	Liver necrosis
48–172	Died—2 days	Liver necrosis
48–205	Survived	Died after Eck fistula with liver necrosis
48–194	Died—2 days	Liver necrosis
48–71	Died—1 day	Liver necrosis
49–1	Died—2 days	Liver necrosis
49–2	Died—1½ days	Liver necrosis
49–3	Died—2 days	Liver necrosis
49–4	Survived	No effect
49–5	Died—1 day	Liver necrosis

served. Of importance, however, may be the observation of aneurysmal dilation of the portal vein between the anastomosis and the liver. Just how far this process will go is unpredictable. To date, liver function and architecture is normal physiologically and microscopically.

The survival of 2 dogs in the series of 10 hepatic artery ligations merely serves to emphasize the extent and variability of the liver's arterial supply described by many previous investigators. Unquestionably the diaphragmatic arteries and the normal and aberrant branches of the common hepatic artery may play an important role in the vascular nourishment of the liver. Simple ligation of the common hepatic artery with preservation of its collateral usually is without effect in dogs. The fact that many of Markowitz's animals were spared following total ligation by use of penicillin emphasized the importance of the development of this collateral and also emphasized the role of arterial blood to the liver in counteracting infection from bacteria absorbed from the intestinal tract.

The unexpected low values of arterial and venous oxygen saturation during intravenous nembutal anesthesia deserve further study. The use of such an anesthetic may be contraindicated in certain experiments relating to the problems of shock.

SUMMARY AND CONCLUSIONS

1. A new method of end to side anastomosis of the hepatic artery to the portal vein has been devised. The details of the technique are described.

2. This arteriovenous fistula has permitted the uneventful survival of all animals when there were no immediate technical difficulties.

3. Eight of 10 dogs died with liver necrosis from ligation of the hepatic artery and its branches without implantation into the portal vein.

4. At the end of 18 months there has been no evidence of mesenteric congestion, increase in portal pressure, or cardiovascular abnormalities in 3 dogs studied.

5. One animal presented some proximal aneurysmal dilation of the portal vein.

6. Oxygen saturations of the portal blood have been significantly raised.

7. Double depletion studies have revealed normal liver function.

8. An opportunity is presented to study liver function with an altered and increased arterial blood supply.

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CHANGES IN THE RATE OF FLOW OF VENOUS BLOOD IN THE LEG DURING PREGNANCY, MEASURED WITH RADIOACTIVE SODIUM

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OBSERVATIONS, recorded in a previous paper, upon women in labor and in the puerperium (Wright, Osborn, and Edmonds, 1949) showed that the average venous blood flow rate was markedly decreased while labor was in progress, but that a normal flow rate had been regained by the fourth to tenth day of the puerperium. We suggested that this was due to mechanical pressure on the large veins as they traverse the pelvis to form the inferior vena cava posteriorly. So striking was the slowing observed in the women during labor that it seemed advisable to determine whether this change occurred only with the commencement of labor, or whether it took place gradually as a result of the increase in abdominal pressure produced by ascent of the gravid uterus.

Method. The technique employed was exactly the same as that used in previous studies (Osborn and Wright, 1949; Wright, Osborn and Edmonds, 1948, 1949). Briefly, a small volume of radioactive sodium^{24}, in sodium chloride solution containing 2 to 10 microcuries per milliliter, was injected under standard conditions of posture, rest, and temperature into one of the dorsal veins of the foot and its passage through the femoral vein at the groin recorded by a suitably placed, screened Geiger-Mueller counter. The impulses from the Geiger-Mueller counter were relayed in such a way that a permanent kymograph tracing was obtained; from this, the moment at which the radioactive sodium reached the groin could be estimated.

Subjects studied. For this series of observations, 61 normal pregnant women, who presented themselves for booking as maternity in-patients, were studied monthly from their first attendance at 6 to 8 weeks of pregnancy until after delivery. As many as possible (28 cases) were seen during the first stage of labor, and all had their foot-groin flow times measured again during the puerperium. Cases with gross varicosities of the veins or with such medical complications as heart disease and diabetes were excluded from this series of observations, but apart from this the cases were consecutive with no attempt at selection.

In order to determine whether the increase observed in the foot-groin flow time was a generalized circulatory phenomenon or whether it was confined to the lower limbs, a further small group of 12 women, who had not been followed throughout pregnancy, had the hand-axilla as well as the foot-groin flow times estimated during labor and once more in the puerperium.

A small group of nonpregnant patients, who had gross ascites attributable to various causes, were also investigated, their foot-groin venous flow times being measured before and after paracentesis; these offered another group whose intra-abdominal pressure was gradually raised. In their case also there was a sudden reduction of intra-abdominal pressure when tapping occurred which was not unlike that occurring in the main group at delivery.

Results. The average flow times in the legs of the group of women are set out graphically for each month of pregnancy, for the first stage of labor and for the puerperium in Figure 1. During the first trimester, the average of the group closely approximated to that found for nonpregnant females of the same age group (Wright, Osborn, and Edmonds, 1949) and no estimation of foot-groin venous flow time fell outside the normal limits. As pregnancy advanced, however, the average flow time for the group increased in a fairly regular manner,

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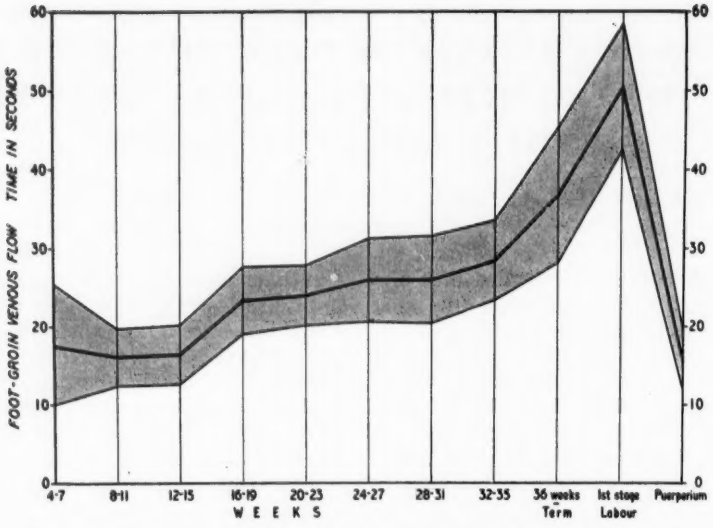

Fig. 1. Average flow times in the legs of 61 women at each month of pregnancy in labor and the puerperium. Shaded area = ± standard error × 3.

and, while the majority of the observations were still well within the normal range, an increasing number in each succeeding month were found to fall outside. Moreover, even when observations on individual cases fell within the normal range, consecutive estimations often showed a progressive slowing as the uterus increased in size. The flow times for a single typical case are shown graphically in Figure 2. As the average flow times increased, the scatter within the group also increased as shown by the changes in the standard errors for each month. These average figures, together with the standard errors of their means and the numbers of cases observed in each 4 week period, are set out in Table I.

TABLE I.—AVERAGE FOOT-GROIN VENOUS FLOW TIMES FOR EACH FOUR WEEK PERIOD IN PREGNANCY, FOR LABOR AND FOR THE PUERPERIUM, EXPRESSED IN SECONDS, TOGETHER WITH THE STANDARD ERRORS OF THE MEANS

Weeks of pregnancy	No. of observations	Foot-groin time—seconds	
4 to 7	10	17.7	± 2.86
8 to 11	52	16.0	± 1.25
12 to 15	63	16.4	± 1.23
16 to 19	66	23.4	± 1.48
20 to 23	61	24.0	± 1.32
24 to 27	60	26.0	± 1.79
28 to 31	57	26.1	± 1.86
32 to 35	63	28.4	± 1.72
36 term	50	36.8	± 2.87
Labor	28	50.3	± 2.69
Puerperium	53	15.8	± 1.25

The average leg venous flow time of 50.3 seconds (with standard deviation of 14.01) obtained for the present group during labor corresponded closely with that found previously (previous series 56.4 ± 10.35 seconds). Return to a normal flow time was also again found to occur in the puerperium, the figure of 15.8 seconds not differing significantly from that of 16.0 seconds obtained for the group in the 8 to 11 week period. Figure 3 shows the individual month to month variations in the 28 primiparous women who were followed throughout pregnancy, in labor, and in the puerperium. It shows the degree of variation of consecutive observations for each patient and the marked increase of the foot-groin flow time in labor, followed by the rapid return to normal after delivery.

Comparative observations made upon both arm and leg venous flow times in 12 women

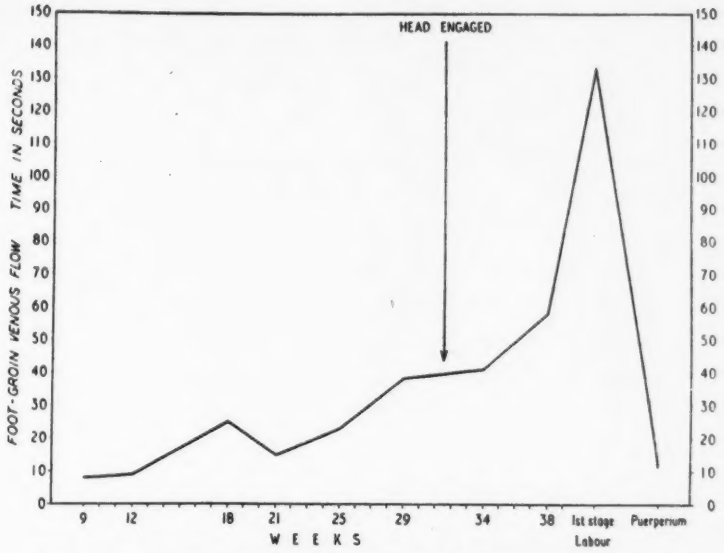

Fig. 2. Mrs. M. Typical case showing progressive increase of the foot-groin flow time during pregnancy and return to normal in the puerperium.

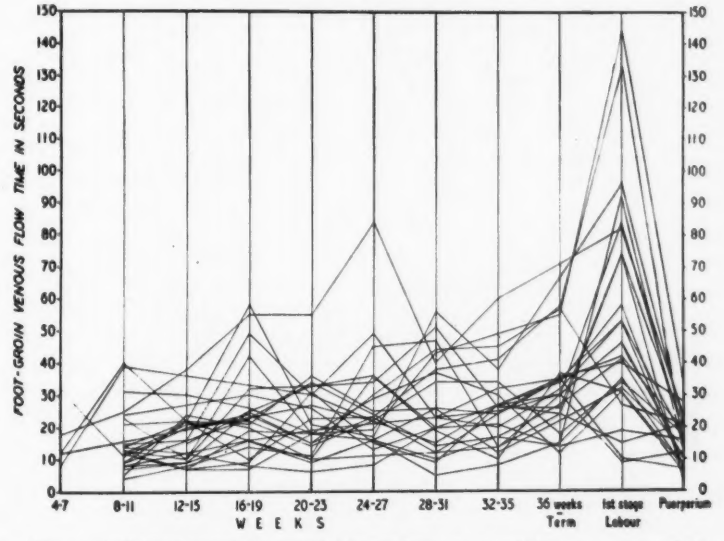

Fig. 3. Individual month to month observations on 28 primiparas seen regularly during pregnancy, in labor and the puerperium.

during labor and again in the puerperium are set out in Table II. To be able to compare directly the two sets of measurements in the same individual, these findings have been expressed as average rates of venous flow in centimeters per second. When the results obtained in the leg were compared statistically, it was found that a strongly significant change in

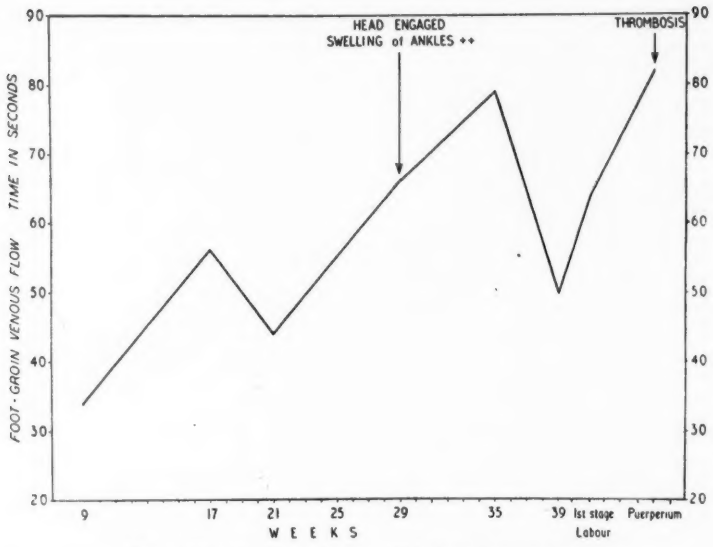

Fig. 4. Mrs. S. Thrombosis on fifth day of puerperium.

the rate of flow had occurred in the two sets of observations ($P<0.01$). Comparison of the arm flow rates, however, showed that the flow rate in the upper limb underwent no significant change ($0.5>P>0.4$). After delivery, the arm and leg rates showed small differences which are insignificant statistically ($0.9>P>0.8$).

DISCUSSION

In a previous paper we suggested that the slowing which occurred in the venous flow in the legs of women in labor was brought about by the mechanical obstruction to the veins in the lower limb by the increased abdominal pressure caused by the gravid uterus and also by the fetal head pressing in the pelvis. The present findings throw further light upon this hypothesis. The increase in foot-groin time was fairly gradual and constant during pregnancy, but it seemed possible that the engagement of the fetal head might cause a secondary obstruction to blood flow. The time at which this takes place varies considerably in different women, occurring in some instances as early as the 28th week of gestation in primiparas, while in multiparas it may be delayed until labor is in progress. It was possible, therefore, that the average figures for the whole group for each month might mask any change in leg flow caused by the descent of the fetus. The first observation, therefore, which was made on each primiparous case after the head was found clinically to be engaged was compared with the last recorded when the head was known to be floating, irrespective of the week of gestation at which engagement occurred. It was found that the average foot-groin time observed at the last time the head was free was 24.4 seconds, while the average for the first observation after it had become engaged was 33.4 seconds. These figures are significantly different ($P<0.01$). Nevertheless a further analysis was thought desirable since the average flow times were found to be grad-

TABLE II.—COMPARISON OF FOOT-GROIN AND HAND-AXILLA RATES OF FLOW TOGETHER WITH THE STANDARD ERRORS OF THEIR MEANS, IN A GROUP OF 12 WOMEN IN LABOR AND IN THE PUERPERIUM, EXPRESSED IN CENTIMETERS PER SECOND

	Foot-groin flow rate—cms./sec.		Hand-axilla flow rate—cms./sec.	
1st stage of labor	2.26	±0.99	10.69	±6.47
Puerperium	7.06	±2.92	11.73	±6.50

ually increased throughout pregnancy. In the same group of cases, therefore, the two last observations before the fetal head had engaged were compared in the same manner. The difference between these sets of figures was found to be much less significant; the averages were 21.9 seconds and 24.4 seconds ($0.10 > P > 0.05$).

A rise in leg venous pressure, measured by direct cannulation during abdominal operations, was reported by Davis and Gilman (1941) who found that it was most marked when the uterus was dragged upon or packed and after the application of abdominal binders. Both these procedures were likely to increase the intra-abdominal pressure, the importance of which upon the control of blood flow in the lower limbs has also been observed by direct pressure measurements by McLennan (1943). This author introduced needles into the anticubital and femoral veins of both normal and pregnant subjects and noted the pressures in these veins with a manometer. He found that, in the arms, the pressure remained the same throughout pregnancy, but that at term there was a slight, though insignificant, rise. In the legs, however, he found a gradual and sustained elevation in venous pressure as pregnancy advanced, the rise being first apparent at the beginning of the second trimester. It is of interest that we noticed the first appreciable increase in foot-groin flow time in the same period. If an increase in intra-abdominal pressure obstructs the blood flow from the lower limbs, then his observations that venous pressure is raised, and ours that venous flow is slowed, would both appear to be dependent upon this common cause.

That the slowing of venous flow rate is confined to the legs and is not a part of a generalized increase in circulation time is shown by the comparison of foot-groin and hand-axilla times, both being measured while the patients were in labor and again after delivery. Manchester and Loube, 1946, confirmed and expanded earlier work (Klee, 1924; Spitzer, 1933; Cohen and Thomson, 1936) and showed that arm-tongue and arm-lung times change very little during pregnancy. None of these authors, however, studied the foot-carotid times so that our finding of a pronounced slowing in the lower limbs is of considerable interest.

As suggested previously, this slowing may be a factor in the onset of venous thrombosis. One patient, who was under observation throughout pregnancy, was of interest in this respect.

Mrs. S., primipara, aged 34 years, had a remarkably long foot-groin flow time during pregnancy (Fig. 4). She had moderate varicose veins, which were rather more severe in the left leg. Swelling of the ankles developed at the time of the engagement of the fetal head but was not accompanied by pain or signs of toxemia. Delivery was normal (first stage, 32 hours; second stage, 1 hour; third stage 20 minutes), a prophylactic episiotomy being performed. On the third day after delivery, however, she had slight pain in the left calf and 2 days later she developed a severe thrombosis of the saphenous vein. For these reasons she has been excluded from the group analyzed in this report. The observation on the foot-groin time in the puerperium was made on the same day that the thrombosis occurred and the injection, being made in the opposite leg, could not have influenced its formation. It was apparent that the prolonged venous flow time had persisted into the period when the other factors in thrombosis, the blood chemical and cytological changes, might be expected to have started to be operative, so that in this woman, all the factors were present at the same time.

This single case, while insufficient on which to base far-reaching conclusions, may well point to the way in which changes in the rate of venous blood flow can influence the onset of postoperative thrombosis.

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THE THORACOABDOMINAL APPROACH FOR RETROPERITONEAL GLAND DISSECTION: ITS APPLICATION TO TESTIS TUMORS

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THE development of the thoracoabdominal approach in recent years can be considered a milestone in the progress of surgery. Due to notable advances in anesthesia and blood replacement therapy within our generation, this precise technique has developed to the point where it has become an integral part of the surgeon's armamentarium. In the field of general surgery, esophageal resection and total gastrectomy have become commonplace as a result of the unparalleled exposure secured through this route (17, 33, 46). Lesions which heretofore would have been considered inoperable have proved surgically amenable when approached in this manner.

We, as urological surgeons, have been impressed by the excellent surgical exposure of the infradiaphragmatic space secured by the thoracoabdominal incision and we have endeavored to adapt it to specific problems of our own. Marshall, Mortensen, and Chute and Soutter have noted the comparative ease with which large renal tumors can be excised through this approach. One of us (W.F.L.) has used this approach for the exploration or removal of renal tumors in 15 cases without death or serious complication. We have recently utilized the technique to great advantage in radical retroperitoneal node dissection for testis tumors and have been so impressed with its advantages that it seems worth while to call it to general attention.

A survey of the literature in reference to the thoracoabdominal approach in surgery reveals a variety of techniques utilized by various surgeons both here and abroad. The method originated in the efforts of Lannelongue and of Micheli to develop a surgical approach to the cardiac portion of the stomach. Actual priority in its use must be given to von Mikulicz who in 1896, as noted by Gottstein, developed a combined thoracoabdominal, extrapleural route for lesions of the lower end of the esophagus and stomach. In the 2 cases cited the integrity of the pleural cavity was carefully preserved. From 1900 to 1910 Mardwedel, Tiegel (48, 49), Wendel, and Janeway and Greene reported modifications of the von Mikulicz concept. In 1933 Ohsawa first evolved a transpleural, thoracoabdominal approach. This was accomplished by a single incision. An oblique abdominal incision was extended dorsolaterally over the seventh intercostal space to the inferior angle of the scapula. This author, therefore, must be considered the first surgeon to convert the pleural and abdominal cavities into a single operative space by division of the diaphragm. Previous to 1942 the abdominal portion of the thoracoabdominal incision had a vertical component in the midline or pararectus area. At that time Wu and Loucks described a thoracoabdominal route coursing along the seventh intercostal space from the infrascapular region, extending medially across the epigastrium to the lateral border of the rectus muscle. This general type of incision is most commonly used at the present time. Humphreys, Garlock (18, 19), and Sweet have developed this transthoracic procedure to its present perfection in the treatment of carcinoma of the esophagus and cardiac portion of the stomach. The greatest impetus to the use of the thoracoabdominal incision originated in the military surgery of World War II where a wealth and diversity of material presented itself. Opportunities to observe the repair of combined abdominothoracic wounds were common and

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experience gained in this field has served to stimulate its use in civilian surgery in the post-war period.

Lymphatic drainage of the testis. A fundamental knowledge of the normal lymphatic drainage of the testis and epididymis is essential in the intelligent treatment of testis tumors. The testis and epididymis have separate and distinct lymphatic channels, the former draining retroperitoneally to those areas concerned in its embryological development, the latter to lymph glands in the region of the external iliac artery and vein.

Present knowledge of the routes of lymphatic metastasis of testis tumors has originated in the anatomical studies of Most, Cuneo (13), Jamieson and Dobson, and Rouviere. Barringer and Earl, Lowry and associates, and Auerbach and associates have contributed significant necropsy data on patients dying of advanced disease. Little, if any, precise clinical observations have been made on lymphatic metastases in the early phase of the disease, before the obvious collateral and retrograde involvement found at autopsy has occurred.

It should be thoroughly understood that there is regional specificity in the lymph drainage of each testis proper. Despite traditional concepts, it is conceivable that lymphatic metastasis is initially ipsilateral rather than bilateral as is commonly taught.

The efferent lymphatic channels arising in each mediastinum testis pass in conjunction with the spermatic vessels through the inguinal canals into the retroperitoneal space where they are in close association to posterior parietal peritoneum (see Figs. 1 and 2). At the point where the spermatic vessels cross the ureter the lymphatic channels veer medially to be distributed to lymph nodes in relation to the aorta, inferior vena cava and renal pedicles. The primary echelon occurs in the region of the embryological development of the testis, namely, the nodes in relation to the renal pedicles, the abdominal aorta and inferior vena cava. In the case of the right testis the most common primary distribution is to the right paracaval, interaortocaval and right renal pedicle nodes; on the left side the paraaortic, preaortic, interaortocaval and left renal pedicle glands are involved. The differential involvement of these various nodal systems is of interest. We cannot summon a sufficiently large number of specific cases to support a dogmatic statement at this time, but we have been observing 2 cases with early metastasis solely to lymph glands at the level of the renal pedicles without involvement of nodes distal to this level. Exact data concerning differential involvement of the primary lymphatic echelon in testis tumors are not in existence.

Secondary lymphatic spread appears when the primary area is heavily seeded by tumor emboli producing considerable mechanical blockage of lymph channels and nodes. Subsequent to this phenomenon, many collateral and retrograde lymphatics are involved resulting in contralateral spread to the opposite lumbar chain and retrograde involvement of the iliac system. Anatomically, direct metastasis to iliac glands can occur only when the primary tumor invades the adjacent epididymis since the normal lymphatic drainage of this organ is to glands situated in relation to the external iliac artery and vein (44).

The autopsy statistics of Barringer (3), Lowry, and Auerbach lead one to believe that, due to the free anastomoses between opposite lumbar lymph chains, contralateral metastases occur early. It is probable, however, that early metastasis occurs in a homolateral fashion, with contralateral spread developing as a later phenomenon after lymphatic obstruction in the glands primarily involved. Lewis has commented on the lack of contralateral node involvement in his series of 169 radical retroperitoneal node dissections for testis tumors. The validity of unilateral retroperitoneal node dissection is dependent upon this point, for in the past the operation has been disparaged in the belief that bilateral metastases are widespread and early. Little if any precise data exist in the literature on the early metastasis of testis tumors and it should be clearly elucidated in the future by repeated clinical observation and record. Opinions which prevail at the present time have largely been developed from necropsy statistics on patients dying of advanced metastatic disease.

TABLE I.—SEMINOMA: SIMPLE ORCHIECTOMY PLUS RADIATION, 5 YEAR SURVIVALS

Author	Percentage 5 year survivals
Barringer, B. S. (2)	56.0
Kelby, G. W., Stenstrom, K. W. (32)	56.0
Leddy, E. T. Am. J. Roentg., 1948, 60: 39	67.7
Sauer, H. R., Blick, W. S. J. Urol., 1949, 62: 69	59.6

TABLE II.—PERCENTAGE DISTRIBUTION OF 922 CASES OF TESTIS TUMOR FROM FRIEDMAN AND MOORE (16)

Tumor type	Per cent	Radiation required per portal
Seminoma	35	1500–1800 r
Embryoma carcinoma	19	2000–4000 r
Teratocarcinoma	35	2000–4000 r
Teratoma	7	Radioresistant
Miscellaneous	3	2000–4000 r
Interstitial cell tumor	1	Radiation not indicated

Origins of retroperitoneal gland dissection. It is notable that surgical advance in the treatment of testis tumors was inhibited until certain fundamental anatomical precepts were established. In 1899 Most comprehensively described the normal lymphatic drainage of the testis and epididymis. In 1901 Cuneo (13) further emphasized the fact that the primary lymphatic echelon of the testis is in the region of the embryologic origin of that organ rather than in the inguinal or iliac glands as had previously been supposed. Prior to this period Stinson had advocated radical orchiectomy with inguinal gland dissection, and Villar (50, 51) had suggested high resection of the spermatic cord with iliac gland dissection. These operations were obviously conceived without knowledge of the primary pathways of lymphatic extension of testis tumors.

As a result of the contributions of Most and Cuneo, surgical effort was directed toward extirpation of the lumbar lymphatic extension of testis tumors. Roberts of Philadelphia in 1901 performed the first recorded retroperitoneal node dissection for testis tumor. He made a transperitoneal approach to the lumbar lymph glands, but his patient succumbed to peritonitis. Several years later in Paris, Gregoire attempted to resect the lumbar glands for testis tumor, but found inoperable disease. This event is notable in that a retroperitoneal approach was utilized for the first time. Later, in the year 1905, Cuneo (14) successfully removed four lumbar glands for testis tumor. One of these nodes showed metastatic disease. These unique operative attempts stimulated Maurice Chevassu, who at that time was preparing his doctoral thesis on "*Tumeurs du testicule*," (6). In 1910 he reported 2 successful retroperitoneal node dissections for testis tumor, and graphically described an extraperitoneal approach along a line drawn from the tip of the tenth rib to the region of the internal inguinal ring (8) (see Fig. 3). His later operative experience (9, 10, 11) paralleled that of Hinman, who, in 1914, wrote the first of a series of brilliant articles on the radical operative treatment of tumors of the testicle (22). At that time he described the experience of the Johns Hopkins Hospital, and advocated resection of lumbar nodes in an attempt to improve the percentage of 5 year survivals. In his subsequent papers (23 to 28) he emphasized the poor prognosis in testis tumors treated by simple orchiectomy alone, noting that 15 per cent of such cases survived 5 years. Tanner in 1922 collected 600 cases of testis tumor, of which 465 were followed postoperatively. Of these, 377 or 81 per cent were dead within 4 years. Twenty-five, or 5.5 per cent, survived 5 years. Realizing these facts Hinman by conclusive statistics demonstrated that he could materially improve the prognosis of the disease by more radical surgical means. In his series of 80 unilateral radical retroperitoneal gland resections reported in 1933, 36 patients had no evidence of lymphatic extension at operation. Eleven of these were living from 1 to 5 years. Only 5 patients were known to be dead. Forty-one patients had positive retroperitoneal nodes at operation. Twenty-three were dead within a year. Seventeen were living, 6 more than 5 years. Cahill, in 1941, reported 18 cases of radical retroperitoneal node dissection for testis tumor, and was of the opinion that his operative results paralleled those of Hinman.

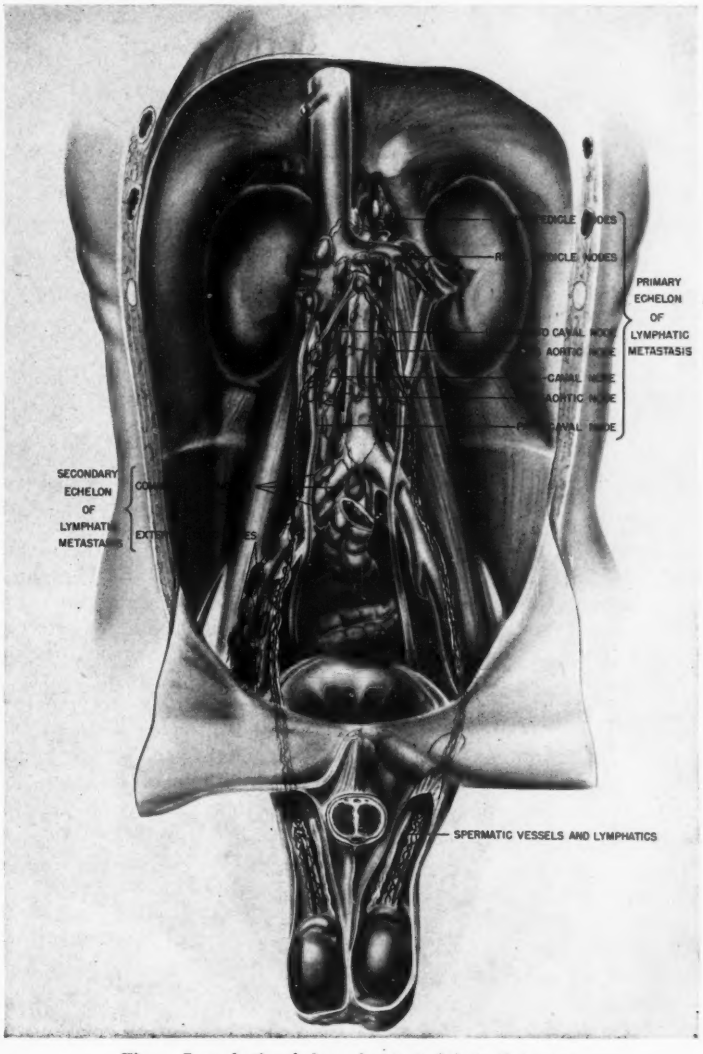


Fig. 1. Lymphatic echelons of metastasis in testis tumors.

The onset of the radiation era in the early 1920's cast a cloud over the radical surgical approach to testis tumors. The apparent successful application of radiation was principally due to the extreme radiosensitivity and predominance of the seminomatous form of testicular tumor. It is now apparent that the radical operation is not indicated in the presence of seminoma, since most clinics (2, 15, 32) report 50 to 70 per cent 5 year survivals with simple orchiectomy and radiation alone (see Table I). However, there remains a large group of the teratomas, teratocarcinomas, and trophoblastic carcinomas which are relatively radioresistant and so potentially curable only by radical surgery (16) (Table II).

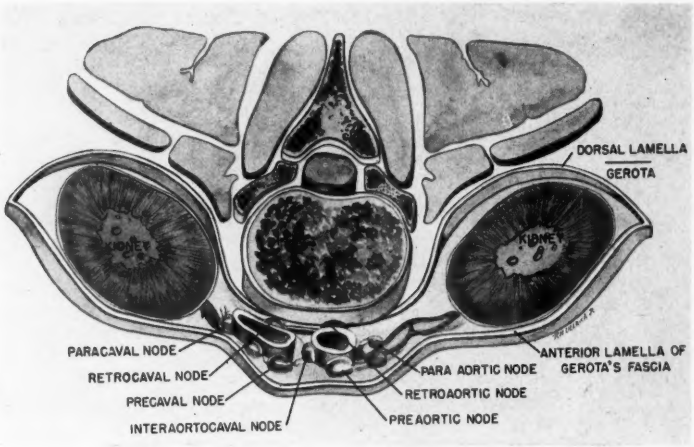


Fig. 2. Relation of Gerota's fascia to retroperitoneal lymph nodes.

The surgical attack on this problem has received added emphasis in recent years through the clinical efforts of Lloyd Lewis at Walter Reed General Hospital and the peerless pathological study of 922 cases of testis tumor from the Army Institute of Pathology by Friedman and Moore (16).

In the past the orthodox surgical approaches of Chevassu (9, 10, 11) and Hinman (28) to retroperitoneal gland dissection have had one specific and obvious disadvantage. The renal pedicle area and infradiaphragmatic space have been inadequately and incompletely exposed. Both authors recognized this fact. Chevassu (11) termed the renal pedicle area "*la zone critique*," and Hinman (25) in 1933 felt that resection of glands should be extended above the renal pedicles. He quoted the experience of Hepler of Seattle who reported a death from metastasis to the suprapedicle area 7 years after a previous retroperitoneal gland dissection in which the entire nodal system distal to the pedicle had been resected without pathologic evidence of disease. In our experience the renal pedicle nodes have been involved by metastatic disease as commonly as those of the lower paracaval, interaortocaval, and para-aortic systems. Two cases are cited later in which no positive glands were encountered below the level of the renal veins.

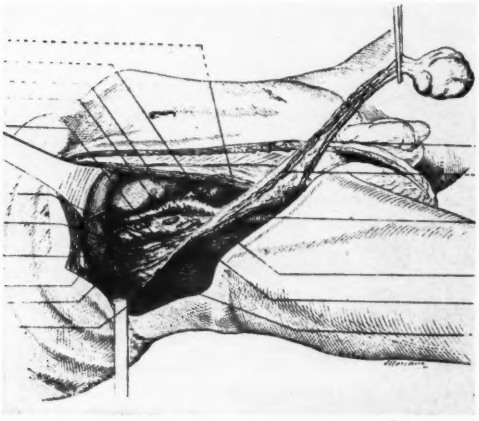


Fig. 3. Original operation as taken from Chevassu.

Hinman (28) described several incisions but preferred that which paralleled the lower border of the twelfth rib coursing anteriorly and inferiorly to the region of the internal inguinal ring. It provides excellent exposure of vessels within the pelvis and the major portion of the aorta and inferior vena cava. As the dissection proceeds superiorly, however, considerably more difficulty is experienced due to the spatial limitations of the incision. If persistent dissection of lymphatic tissue in relation to the renal pedicles is carried out in the presence of this handicap, the risk of vas-

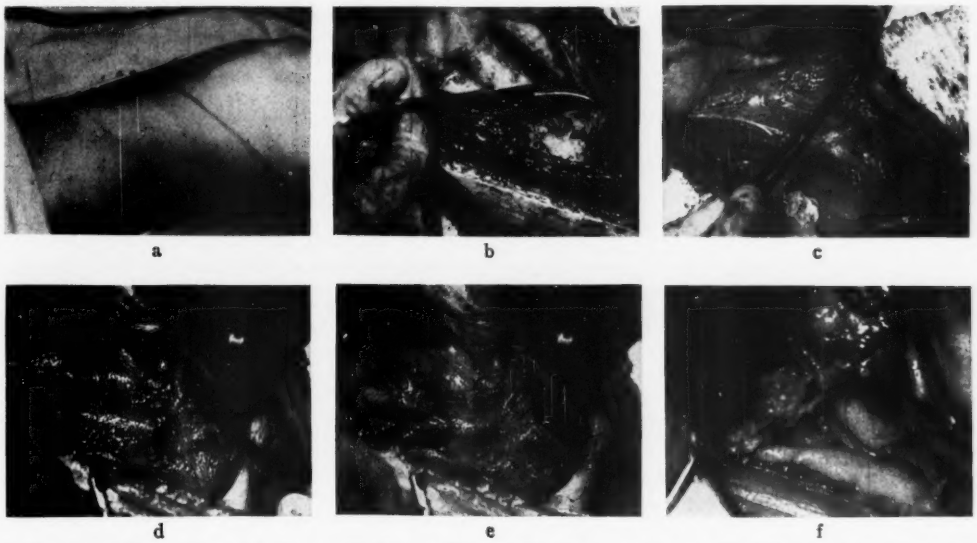


Fig. 4. a, Incision over 10th rib. b, Division of diaphragm. c, Positive nodes at level of renal pedicle. d, Dissection of renal vessels. c, Dissection of para-aortic nodes. f, Mass of nodes dissected from great vessels.

cular accident is increased and a complete dissection is impossible.

We have modified the orthodox incision of retroperitoneal node dissection by extending it to form a combined thoracoabdominal incision. The approach is begun in the posterior axillary line over the tenth rib and is carried anteriorly and inferiorly over this structure into the abdomen. The extent of the incision can be varied but it is usually carried deep into the lower quadrant to a point midway between the internal inguinal ring and the lateral border of the rectus muscle. In this fashion splendid exposure of the infradiaphragmatic space, renal pedicle areas, aorta, inferior vena cava, and iliac vessels is secured. The additional exposure superiorly is of great importance in a complete extirpation of the primary site of metastasis in carcinoma of the testicle. In addition, the inferior extension of the incision allows dissection of the external iliac nodes, thus permitting complete dissection of the lymph glands from the level of the crus of the diaphragm to the femoral canal. It is theoretically an advantage to begin the gland dissection proximal to the primary site of metastasis.

The advantages of the thoracoabdominal incision for lesions of the spleen have recently been discussed by Carter and for the kidney by Mortensen, and Chute and Soutter. The latter have emphasized the ease of exposure of large renal neoplasms through this route. We believe also that the approach is of inestimable value in the treatment of carcinoma of the testis when radical retroperitoneal gland dissection is indicated. There are several obvious advantages over previous more orthodox routes. Primarily, there is the wide exposure of lymph nodes in relation to the renal pedicles and the contiguous great vessels which form the primary echelon of lymphatic metastasis in testis tumors. The accessibility of these structures is thereby enhanced and one is able initially to attack the primary site of metastasis, subsequently carrying the dissection distally to include secondary lymphatic foci of disease.

TECHNIQUE OF OPERATION

The approach is made under positive pressure, inhalation anesthesia with the patient in the usual kidney position, the body rotated 10 degrees posteriorly. Incision is made over

the tenth rib from the posterior axillary line to the costochondral junction and extended obliquely down into the lower quadrant of the abdomen to a point midway between the internal inguinal ring and the lateral border of the rectus muscle. The tenth rib is resected and the pleural and retroperitoneal spaces opened. The diaphragm is divided for a distance of 10 to 12 centimeters dorsolaterally, providing ready access to the retroperitoneal space after mobilization of peritoneum and Gerota's fascia from the under surface of the diaphragm (see Fig. 4). The retroperitoneal gland dissection is carried out en bloc within Gerota's fascia anterior and posterior to the renal pedicles from the level of the crus of the diaphragm to the internal inguinal ring, including all the lymph nodes in relation to the great vessels. It is evident that when extension to retroaortic or retrocaval glands is found, inoperability must be considered. However, we have found that careful retraction and dissection will allow the surgeon to resect a majority of these nodes. Ligation of large lymph channels when encountered is necessary to obviate lymph fistulas. Closure of the incision is made in an anatomical fashion, the silk technique being used without drainage. In our hands this mode of retroperitoneal node dissection for carcinoma of the testis has proved most satisfactory and easy of execution. We have limited the operation to those cases of testis tumor which are radioresistant and without palpable evidence of regional node metastasis.

CASE REPORTS

To emphasize the transition we have made from the conventional incision of Hinman and Chevassu to the thoracoabdominal approach, 4 specific cases are presented.

CASE 1. This 23 year old patient presented a small 2 centimeter primary lesion of the right testis which proved to be a primitive type of trophoblastic carcinoma. Initially retroperitoneal node dissection was accomplished through an orthodox Hinman incision with a lumbar extension. There was great difficulty in securing enough exposure to resect lymph nodes in relation to the right renal pedicle. Dissection of positive nodes along the great vessels from a point 1 centimeter below the renal pedicle was unimpeded, however. At operation widespread contralateral node metastasis was noted and at a second stage the nodes on the left side were completely resected through a thoracoabdominal incision securing a complete chain of lymph nodes from the left crus of the diaphragm to the external iliac level. In view of the original inadequate dissection of the right infradiaphragmatic space, at a later date this area was explored transthoracically, and one additional, 3 centimeter, positive node was removed at the level of the right renal pedicle in the most proximal portion of the interaortocaval area.

Patient was admitted to the West Roxbury Veterans Hospital for the first time on December 27, 1948, because of swelling of the right testicle of 3 months' duration. Three months prior to admission the patient noted onset of mild swelling and tenderness in the right testicle associated with generalized malaise, nausea, and vague abdominal pain.

Physical examination revealed temperature normal; blood pressure, 116/72; heart and lungs normal; abdomen, negative. No masses could be felt. In the lower pole of the right testicle was a 1 centimeter firm mass which was somewhat tender. Penis and left testis were normal.

Laboratory examination revealed the serology, negative; white blood cells, 8,700; hemoglobin, 80 per cent; urine, acid with specific gravity 1.027, negative for albumin and sugar, one to three white blood cells in the sediment. Urine culture was sterile. The nonprotein nitrogen was 35 milligrams per cent. X-ray examination of the chest revealed no evidence of active pulmonary pathology or metastatic disease. An Aschheim-Zondek test was negative.

On the day following admission to the hospital an x-ray examination of the scrotum was made, which revealed a small area of calcification in the right testicle. Two days after admission a right orchiectomy was done, the cord being ligated at the internal inguinal ring. Examination of the gross specimen revealed the mass to involve the seminiferous substance in the lower third of the right testicle and pathological examination revealed a trophoblastic carcinoma. Because of the pathology demonstrated it was felt that a radical retroperitoneal dissection of the area of lymphatic drainage of the testicle was indicated. An intravenous pyelogram was made which showed a normal upper urinary tract and a questionable displacement of the right ureter in its middle third. On the tenth hospital day, through an incision running from the right costovertebral angle to the right groin, the retroperitoneal area was exposed and found to contain multiple nodes grossly positive for metastatic tumor. These were completely removed from the external inguinal ring to the level of the renal pedicle on the right. At the time of the operation the left side of the great vessels was palpated and enlarged nodes were discovered. Following operation the patient made a comparatively uneventful recovery. The wound healed primarily and in view of his excellent condition it was felt advisable to dissect the nodes on the left side of the great vessels. This was carried out on his twenty-fifth hospi-

tal day through a thoracoabdominal approach and resection of the anterior half of the tenth rib. At this operation the complete lymphatic chain from the diaphragm to the external inguinal ring on the left was removed en bloc. During the course of the dissection the inferior mesenteric artery was clamped and carried away with the bloc dissection, but at the close of the operation the descending colon and sigmoid were inspected and found to be completely viable and with good arterial pulsation. Following the second operation the patient again made an uneventful recovery, showed complete expansion of his lung throughout his postoperative course, was only mildly distended for 2 to 3 days following the operation and again healed primarily. At the time of the second operation palpation of the lymphatic chain on the right side of the great vessels above the right renal pedicle revealed a large node and questionable other nodes in that area. It was felt that the first operation on the right had been incomplete because of inadequate exposure, and it was further felt that a thoracoabdominal approach to the region of the right renal pedicle was indicated in order to remove these nodes. On his forty-sixth hospital day, 16 days after his second node dissection, a thoracoabdominal approach was made to the region of the renal pedicle on the right and one large 3 centimeter node was found at the level of the left renal vein between the vena cava and the aorta. This was removed. His mediastinum was palpated and found to be free of any gross metastatic disease and no other evidence of gross lymphatic metastases could be felt. He again made an uneventful recovery. His lung remained completely expanded on the right throughout his convalescence and in spite of the extensive surgical procedures his hemoglobin and total protein remained within normal limits. Thirteen days following his last node dissection he was started on deep x-ray radiation to both the abdominal and mediastinal areas receiving 400 roentgens daily, this in an attempt to control any microscopic metastases which could not be discovered at the time of operation. After 12 daily treatments of 400 roentgens totaling 4,800 units, the patient was sent on leave of absence to return daily to the X-ray Department for this therapy. He will continue this until he has had a proposed total of from 20,000 to 24,000 roentgens. He has done remarkably well in spite of his extensive metastatic disease, and it is hoped that with the combined efforts of surgical removal and x-radiation effective palliation may result.

Diagnosis: trophoblastic carcinoma, right testis, with extensive bilateral retroperitoneal lymphatic metastasis (33 of 36 nodes positive).

Operations: right orchiectomy, December 29, 1948; radical retroperitoneal node dissection, right (Hinman) January 7, 1949; radical retroperitoneal node dissection, thoracoabdominal, left January 21, 1949; retroperitoneal node dissection, right, thoracoabdominal approach, February 11, 1949.

CASE 2. This 31 year old patient presented a primary tumor in the right testis which proved to be teratocarcinoma. He was first operated upon on the right side through a typical Hinman approach from the tip of the tenth rib down to the internal inguinal ring. Twenty-six nodes were resected, a single lymph node, the highest node in the chain, proving positive. The same difficulty was experienced as in Case 1 with dissection at the level of the renal pedicle. No contralateral spread was evident, but in view of the location of the positive node, an exploration of the right infradiaphragmatic space was effected through a thoracoabdominal incision and 7 additional nodes were resected, 2 of which proved positive. Nine months after operation this patient is living and well.

This was the first West Roxbury Hospital admission of a 31 year old white male, meat selector, with a complaint of a swollen right testis of 2 months' duration. Testis was previously normal and had gradually increased in size and hardness with minimal tenderness.

Physical examination showed a well developed, well nourished man in no acute distress. The right testis was 2 times normal size, hard and firm. No abdominal masses were palpable.

Laboratory examinations revealed serology, negative; urine, concentrated to 1.021, sediment containing a few epithelial cells and occasional white blood cells; white blood counts ranged from 5 to 11,000; hemoglobin was 87 per cent; nonprotein nitrogen was normal. Aschheim-Zondek test in all dilutions was negative. Chest showed no evidence of active pulmonary pathology or metastatic disease.

On the second hospital day a radical right orchiectomy was done. Pathological examination of the specimen showed a teratocarcinoma. On the seventh hospital day a radical right retroperitoneal node dissection, Hinman type, was done and a chain of 26 lymph nodes was removed. Sutures were removed on the eighth postoperative day. The patient developed superficial wound sepsis at the lower portion of the incision and a draining sinus at the upper midportion of the incision. The infection cleared up rapidly, while the patient continued to drain from the sinus until the twenty-first postoperative day. Only one of the lymph nodes excised was found to contain tumor and on review of his case it was decided to extend the dissection through a thoracoabdominal approach. Consequently, the patient was placed on leave of absence for convalescence. Surgery was deferred until return to the hospital because of superficial sepsis in both ends of the abdominal incision, which was prolonged because of foreign body reaction around the silk sutures.

Finally, on March 15, 77 days after the original admission to the hospital, a right retroperitoneal node dissection was carried out through the thoracoabdominal approach and seven nodes were removed from the renal pedicle area. Two of these were reported positive. Sutures were removed on the eighth postoperative day. The incision healed well. The patient was bothered by costal nerve pain, relieved by eucupine block. As further prophylaxis he was started on x-ray therapy of the retroperitoneal area,

which he tolerated well, and was finally sent on leave of absence on April 18 to continue with x-ray therapy as an out-patient.

Diagnosis: teratocarcinoma of the right testis with retroperitoneal node metastasis to 3 of 33 nodes.

Operations: radical orchiectomy, right, December 30, 1948; radical retroperitoneal node dissection (Hinman), January 4, 1949; exploration of right infradiaphragmatic space, thoracoabdominal approach, March 15, 1949.

Thus, Case 1 and Case 2 point out the limitation of the Hinman incision in contrast to the thoracoabdominal approach in which exposure of the infradiaphragmatic space is ideal. Case 1 also emphasizes the necessity for bilateral retroperitoneal gland dissection in selected cases.

CASE 3. This 25 year old man presented himself with a seminoma of the left testis, histologically, but with a positive Friedman test. In view of the latter we felt that some trophoblastic element was present. Although it could not be histologically identified, a left retroperitoneal node dissection was, therefore, performed through a thoracoabdominal incision with resection of the paraaortic and interaortocaval lymph nodes from the level of the left crus of the diaphragm to the external iliac nodes. Thirty-two nodes were resected and 1 positive node was found at the level of the left renal pedicle. Multiple sections of the spermatic vessels were negative for tumor. At present, 6 months postoperative, this patient is living and well.

This 25 year old white male was admitted to the West Roxbury Veterans Hospital for the first time on March 10, 1949, for x-ray treatment to the abdomen for seminoma of the left testicle. Six to 8 weeks prior to this admission the patient noted that his left testicle had become somewhat tender and enlarged. He was seen by his local physician who treated him symptomatically with relief of the swelling and tenderness but the symptoms recurred in about 3 weeks. This time he was seen by a urologist who was of the opinion that the patient had a tumor of the left testis and performed an orchiectomy on March 3, 1949. The pathology report revealed a seminoma of the testicle and he was referred for x-ray therapy.

Physical examination revealed normal temperature; heart and lungs within normal limits; the abdomen essentially negative. No masses were felt. The genitalia were normal except for an absent left testicle and a healing scar on the left scrotum. There was a moderate sized indurated mass in the left groin. The rectal examination was normal.

Laboratory examinations revealed urine, acid, specific gravity 1.027, negative for albumin and sugar with a few white blood cells in the sediment; white blood count, 10,000; red blood count 3,700,000; hemoglobin, 77 per cent. Serology was negative. The nonprotein nitrogen was 45 milligrams per cent. Total protein was 8.2—albumin, 5.7—globulin, 2.5. Urine culture showed Staphylococcus albus. X-ray examination of the chest revealed no evidence of metastatic disease.

An intravenous pyelogram was made which revealed a normal upper urinary tract. A telephone report from the Malden Hospital revealed that the patient had had a positive Aschheim-Zondek test prior to orchiectomy. A microscopic section of the specimen was obtained, and the pathologist at this institution made a diagnosis of seminoma. Because of the reported positive Aschheim-Zondek test, it was felt that the patient must have a mixed tumor in the testicle with embryonal cell elements and therefore a retroperitoneal node dissection was indicated. This was carried out on his eighth hospital day. The lymph nodes from the left internal inguinal ring to the left crus of the diaphragm were dissected. Thirty-two nodes in all were removed. One at the left renal pedicle was positive for metastatic seminoma. The operative approach was of the left thoracoabdominal type, the tenth rib being resected. The patient made an uneventful recovery. The wound healed and sutures were removed on the seventh postoperative day and on the eleventh day deep x-ray therapy was started in the retroperitoneal area.

Diagnosis: mixed tumor, left testicle. Treated. Improved. Metastasis to one left retroperitoneal lymph node.

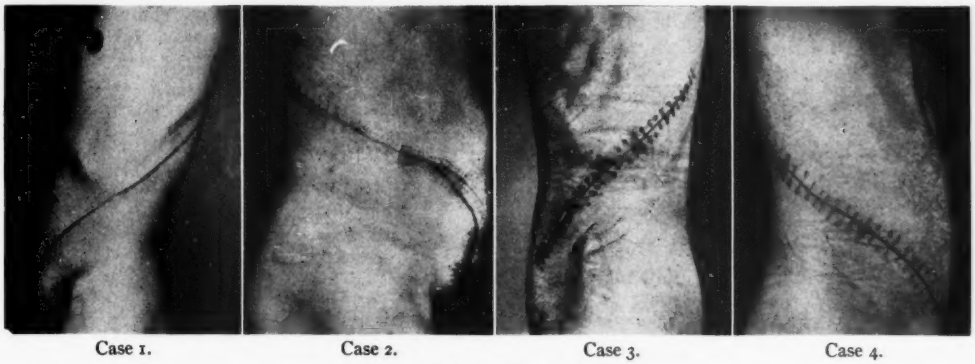
Operation: left retroperitoneal node dissection, thoracoabdominal route, March 18, 1949.

CASE 4. This was an unusual case of bilateral teratocarcinoma of the testis. In 1945 while in service patient developed a teratocarcinoma of the left testis for which he received a left retroperitoneal node dissection plus radiation at the Walter Reed General Hospital. In February, 1949, he reported to the Veterans Administration Hospital, West Roxbury, with a mass in the remaining testis of 3 weeks' duration. This lesion proved to be identical with the original tumor. A right radical retroperitoneal node dissection was accomplished through a thoracoabdominal incision over the tenth rib. Twenty-two nodes were resected and all were negative for metastatic tumor. He manifested no edema despite the bilateral node dissection. It is now 8 months since operation and he is living and well.

This 40 year old white male was admitted to the West Roxbury Veterans Hospital for the first time on February 16, 1949, because of a swelling of the right testicle of 3 weeks' duration.

Three weeks prior to admission the patient noticed a small, hard mass in the right testicle which was not associated with pain or other symptoms. Because of his pertinent past history, he sought medical attention shortly after noticing this mass.

His past history revealed that in April, 1945, while on active duty with the Army in Italy, he discovered a mass in his left testicle which was explored and orchiectomy done. Pathological report was embryonal cell carcinoma of the testicle. He was re-



Case 1. Case 2. Case 3. Case 4.

Fig. 5. Postoperative incisions.

turned to Walter Reed General Hospital where a radical retroperitoneal node dissection was done on the left side, following which the patient had deep x-ray therapy to the retroperitoneal area, the total dosage being unknown at this time.

Physical examination revealed temperature normal; blood pressure 128/76; heart and lungs, normal, abdomen negative except for atrophic radiation changes in the skin on the anterior abdominal wall and over the back. There were no palpable masses. A scar was noted running from the tip of the eleventh rib on the left to the lower end of the rectus muscle. A mild hypospadias was noted with a slight chordee. The left testicle was absent. The right testicle revealed a 1 centimeter mass in the lower pole which was not tender but quite firm.

Laboratory examinations revealed white blood count, 6,400; hemoglobin, 78 per cent; urine, acid, specific gravity 1.022, albumin, sugar, and sediment negative. The serology was negative. The nonprotein nitrogen was 28 milligrams per cent. X-ray examination of the chest revealed no evidence of pulmonary pathology.

An x-ray of the scrotum showed no evidence of calcification. A few days after admission to the hospital a right orchiectomy was done. The pathology report was teratocarcinoma measuring 1 centimeter in diameter. It was felt that retroperitoneal node dissection was indicated, and this was carried out on his eighth hospital day through a thoracoabdominal approach. The entire chain of nodes from the diaphragm to the internal inguinal ring on the right was excised. The patient made an uneventful recovery. Repeated examinations of his chest revealed the lung to be expanded. The wound healed primarily, the sutures were removed on the seventh postoperative day, and the patient was completely ambulant during his entire convalescence. He was placed on 10 milligrams of methyl testosterone daily, as substitution therapy. Discussion with the radiologist revealed that he had had maximum therapy on his previous radiation and would not be able to withstand further treatment.

Diagnosis: teratocarcinoma, right testicle, treated, improved.

Operations: right orchiectomy, February 18, 1949; radical retroperitoneal node dissection, right, thoracoabdominal approach, February 25, 1949.

All the above cases made uneventful recoveries. There were no pulmonary complications and no instances of lymphedema (Fig. 5).

CONCLUSIONS

1. The validity of radical retroperitoneal gland dissection in the treatment of testis tumors must not be considered disproved, since heretofore operations have been generally unilateral and incomplete.

2. We believe that testicular tumors, other than seminomas, should have as complete retroperitoneal gland dissections as possible. If enlarged contralateral nodes are palpable, and this can be determined at the first operation with considerable accuracy, dissection of the opposite side should be performed without delay.

3. The adaptation of the thoracoabdominal approach for retroperitoneal gland dissection in carcinoma of the testis has provided excellent exposure of renal pedicle and infradiaphragmatic areas in comparison to previous conventional incisions of the type originally described by Hinman and Chevassu.

4. The scope and extent of retroperitoneal gland dissection has, therefore, been increased, as is true also of the efficiency, safety, and thoroughness of the procedure. Four cases are cited in point.

5. The patients tolerate the operation exceedingly well. No unusual pulmonary complications have been encountered.

6. There have been no instances of postoperative lymphedema even though 2 of our patients have undergone bilateral node dissections.

7. We believe this modification of the surgical approach to retroperitoneal node dissection in carcinoma of the testis to be of considerable additional aid in the treatment of this disease. It is hoped that interest in this procedure will allow accumulation of data to prove or disprove its effectiveness.

8. It is suggested that this technique may be applicable to other malignant abdominal conditions, such as carcinoma of the kidney, bladder, and lesions of the female internal genitalia.

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EDITORIAL

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THE SURGICAL TREATMENT OF HYPERTENSION

THE treatment of hypertension by sympathectomy was first undertaken by Adson in an effort to determine whether the uniformly fatal course of so called malignant hypertension could be favorably modified by therapy of this sort. In describing their experiences with the first two patients to be treated in this manner, Rowntree and Adson[1] stated that it was their hope that sympathectomy would result in a relative freedom from vascular spasm in the denervated area, that this might result in lowering of blood pressure levels and provide simultaneously an area of diminished resistance which would give way under strain and thereby serve somewhat in the capacity of a safety valve for the protection of the cerebral and retinal vessels.

During the 25 years that have elapsed since this original attempt to modify the course of hypertensive cardiovascular disease, a number of surgeons have become interested in this problem and have carried on clinical investigations in collaboration with their medical associates. The reports of Peet, Craig, Grimson, Hinton, Ray, Poppen, deTakats as well as those of many other authors indicate the widespread interest which has been taken in this problem. Various surgical techniques have been developed to denervate large vascular areas in an attempt to decrease the peripheral resistance to blood flow and to lessen the severity of upward fluctuations of blood pressure which result from reflex vasoconstriction in the normally innervated hypertensive patient. Some observers believe that the inhibition of reflex secretion of epinephrine and the stabilization of blood flow through the denervated visceral vascular bed, the kidney in particular, are equally, if not more, important effects of splanchnicectomy. These physiologic effects probably do occur but have not been clearly demonstrated as yet and hence are presumptive in nature.

There is now abundant evidence that operations of this sort have resulted in favorable changes in the cardiovascular status of many hypertensive patients. Reduction of blood pressure levels, lessening of the severity of reflexly induced elevations of blood pressure, favorable changes in the retinal, cardiac, and renal areas, as well as relief of symptoms for varying periods of time and in varying percentages of patients, have all been reported. One might reasonably expect, therefore, that in many patients the course of the disorder has been favorably affected and that life expectancy has been significantly prolonged. It has not been demonstrated to the complete

[1] ROWNTREE, L. C., and ADSON, A. W. Bilateral lumbar sympathetic neurectomy in treatment of malignant hypertension; report of case. J. Am. M. Ass., 1925, 85: 959–961.

satisfaction of everyone that this is so and under what circumstances it pertains. A significant reduction in mortality rates is the real test of any therapeutic measure for this disorder as recently emphasized by Craig[2].

To the uninitiated, it might seem as though surgical treatment should have been evaluated by this time. The problem is extremely complex. We are dealing with a chronic disorder of unknown origin which takes many years to develop. While a good deal is known about its natural history, the numerous variable manifestations make it difficult to divide patients into clear cut clinical groups so that the prognosis for a particular patient untreated or treated medically can be properly assessed. Accurate control data are essential to the evaluation of any therapeutic measure.

Keith, Wagener, and Barker of the Mayo Clinic were the first to recognize this fact, and in an outstanding contribution in 1939[3] demonstrated that hypertensive patients could be divided into four groups, the prognosis for each being distinctly different. They followed a series of 219 medically treated patients for 5 to 9 years and found that 91 per cent of the patients were dead at the end of the period of observation. The mortality rates for the four different groups varied from 40 to 99 per cent. This report emphasizes how widely the prognosis varies for hypertensive patients. It also indicates that the disorder may be very serious and that the need for modifying the outlook for these patients is great. Prior to and since the report of Keith, Wagener, and Barker, numerous publications have dealt with the prognosis for hypertensive patients. The mortality rates over 5 to 10 year periods of observation have varied greatly and have been as low as 28 per cent. However, these patients were not subdivided into more comparable groups in which important variable factors which influence prognosis were held constant. Unless this is done, confusion will continue to exist regarding the outlook for a particular patient and the need for specific therapy will not be appreciated. More recently Palmer, Loofbourow, and Doering have published control data[4] on a series of 430 medically treated hypertensive patients followed for an average period of 8 years. The cases were divided into 4 grades, using criteria which differ somewhat from those of Keith, Wagener, and Barker. The mortality rate for the group was 61 per cent and varied from 22 to 94 per cent in the different grades. These data are also helpful in evaluating surgical therapy but are not as valid statistically as the Keith, Wagener, and Barker data because of the unfortunate use of an average follow-up period of observation.

In spite of the many reports of results of surgery in the treatment of hypertensive cardiovascular disease which have appeared in the literature, only two have dealt with adequate numbers of cases followed for 5 to 10 or more years. The first was by Peet and Isberg[5] and the second by the author[6]. My associates and I have divided our cases into groups or grades conforming as closely as possible with the criteria of Keith, Wagener, and Barker and of Palmer, Loofbourow, and Doering. We have also devised a plan for dividing hypertensive patients into 5 groups in each of which many variable factors encountered in this disorder are held constant. This increases the likelihood that the patient material contained within each group is more comparable. We have compared the mortality rates for our

[2] Craig, W. McK. Evaluation of treatment of hypertension. J. Am. M. Ass., 1949, 139: 1239–1245.

[3] Keith, N. M., Wagener, H. P., and Barker, N. W. Some different types of essential hypertension; their course and prognosis. Am. J. M. Sc., 1939, 197: 332–343.

[4] Palmer, R. S., Loofbourow, D., and Doering, C. R. Prognosis in essential hypertension; eight-year followup study of 430 patients on conventional medical treatment. N. England J. M., 1948, 239: 990–994.

[5] Peet, M. M., and Isberg, E. M. Surgical treatment of essential hypertension. J. Am. M. Ass., 1946, 130: 467–473.

[6] Smithwick, R. H. Continued hypertension; prognosis for surgically treated patients. Brit. M. J., 1948, 2: 237.

cases with those of the authors referred to, group for group and grade for grade. The results indicate quite clearly that the prognosis for many hypertensive patients has been significantly improved by surgical treatment. We have estimated what the mortality rates would have been for the patients contained in each of our five groups on the basis of the calculated mortality rates for these same patients when grouped or graded according to the methods of the authors quoted. We have also compared the mortality rates for our own surgically and nonsurgically treated patients group for group. The findings indicate that both on the basis of estimated and actual mortality rates, the prognosis for patients contained in our groups 4 and 5 has not been improved. Surgery seems contraindicated in such patients. These are the most advanced cases and patients are either in a near terminal stage or have hopelessly irreversible forms of the disorder. On the other hand, patients in our groups 1, 2, or 3, appear to have benefited greatly by surgical therapy. The details of our classification and those of the authors referred to have been recently published.[7, 8]

Surgery should not be regarded as a cure of hypertensive cardiovascular disease. It is, however, a useful adjunct in the management of this disorder to be used when it is most effective. Special diets and new drugs are also being evaluated as therapeutic measures. To be effective, treatment must be shown to influence mortality rates over long periods of time. It is our impression that surgically treated patients respond better to medical regimen, and that the best results in the long run will be obtained in those patients who have the benefit of what both medicine and surgery have to offer.

[7] SMITHWICK, R. H. An evaluation of the surgical treatment of hypertension. Bull. N. York Acad. M., 1949, 25: 698–716.
[8] SMITHWICK, R. H. The surgical physiology of hypertension. Surg. Clin. N. America, 1949, Dec., 1699–1730.

There still are disagreements about the extent of the surgical procedure. It is my belief that a thorough denervation of the splanchnic bed such as is obtained by removing the sympathetic trunks bilaterally from the eighth thoracic to the first lumbar ganglia inclusive together with the splanchnic nerves is the procedure of choice for most cases. I seriously question the advisability of more extensive procedures. In certain cases, those with coronary heart disease and angina pectoris, removal of the sympathetic trunks and splanchnic nerves from the inferior cervical to the twelfth thoracic ganglia inclusive appears to be preferable to thoracolumbar splanchnicectomy. Also, in patients with unusually rapid heart rates, particularly those with postural tachycardia, removal of the sympathetic trunks and splanchnic nerves from the second to the twelfth thoracic ganglia inclusive appears to be indicated. However, more extensive primary procedures than those which have been mentioned are not advisable in the opinion of the author.

Surgery appears to have a real place in the management of the more severe forms of hypertensive cardiovascular disease. It should not be reserved as a last resort. The indications and contraindications are being clarified and should be well understood in the not too distant future. The management of the hypertensive patient should be a collaborative medical and surgical enterprise. Surgery should be undertaken only by those who are adequately trained in this field and should not be employed promiscuously as just another operation. If the proper procedure is performed in carefully selected cases the benefits will greatly outweigh the untoward effects and will justify through increased life expectancy the discomfort, expense, and the period of disability which major surgery of this sort entails.

REGINALD H. SMITHWICK.

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THE ILLUSTRATION OF HUMAN ANATOMY BEFORE VESALIUS

RUTH B. COLEMAN, A.B., Chicago, Illinois

THE publication in 1543 of the great *Fabrica* of Andreas Vesalius ended for medical science a twelve hundred year period of blind subservience to ancient dogma and tradition. With scalpel and pen and aided by the excellent artist Jan Stephan Van Calcar, Vesalius successfully overthrew the authority of Galen, revolutionizing for all time the teaching of human anatomy. His work served to clear away the morass of confusion and half-truth concerning the structure and function of the human body which had been jealously guarded for so long; it gave to his successors an approach to investigations in anatomy, surgery, and physiology based on scientific method and observed fact.

ANATOMICAL ILLUSTRATION

The period preceding this milestone in the history of medicine and anatomy begins in antiquity at a point difficult to determine without first stating what we mean by *Anatomical Illustration.* There is, for instance, the tiny 4½ inch limestone statuette known as the "Venus of Willendorf" which was found near the village of Willendorf on the Danube in 1908. Geologists and anthropologists place her in the middle Aurignacian Period, 40,000 to 16,000 B.C. She is among the earliest known representations of the human figure. She *illustrates* anatomy, the conception of it held by an unknown artist in the distant past, but she could be called an anatomical illustration only in the broadest sense of that term. In its most comprehensive meaning anatomical illustration is the delineation of the internal or external anatomical structure of man in part or in its entirety, with any one of many possible and quite different motives or intentions. It is generally approached from one of two distinct points of view. Choulant defines these as: "(1) the aid rendered to anatomic science by the graphic arts; (2) the aid rendered to the graphic arts by anatomic science." Streeter and Garrison offer another classification of the same subject: "(1) anatomical illustration without (didactic) intention, (2) anatomical illustration with intention" (4, p. 370). The "Venus of Willendorf" undoubtedly belongs in the first group along with the bulk of sculpture and painting through the ages, the primary purpose of which was *not* the teaching of the anatomy of the human figure but rather the use of the human figure in the graphic expression of ideas.

Choulant goes further to classify the second group (anatomic illustrations of didactic intention) into three principle categories, i.e. the purely schematic, the exact representation of a particular subject, and the ". . . ideal human figure constructed from the constant mean proportion of several types."

The first or schematic type of illustration "attempts to present in outline form the main characteristics of one or more parts" (4). It either purposely disregards an exact knowledge of form or else assumes that the observer already possesses such knowledge and furnishes him with an aid to memory, a simplified expression of the essential elements in the subject being illustrated. This type of illustration was widely used in the pre-Vesalian period when a precise knowledge of human anatomy was lacking. It is just as widely used today in the teaching of medicine, not because of a dearth of anatomic fact or understanding but in order to elucidate structural and physiologic principles in a direct and simple manner, unencumbered by the irrelevant and often confusing detail of more realistic forms of expression.

From the Department of Medical Illustration, The University of Illinois.

The second type of anatomical illustration, the exact representation of a particular subject, pictures an individual subject in all its details, just as it is found in nature. "This method of representation disregards the fact that each internal organ, like the countenance or other externalities, is based upon a common ideal type which conditions its form; on the other hand, in each individual this type presents peculiar deviations from the normal which do not accord with the generic form but serve to make it individually distinctive, and which must therefore be disregarded when the true type is sought" (4). This type of illustration is found particularly useful today in the study and recording of pathological anatomy where individual instances of rare and abnormal forms of organs and tissues are to be shown.

The development of the third or ideal type of anatomic illustration ". . . corresponds with the growth of the science of anatomy in all its periods" (4). It "presupposes a vast amount of previous labor and cannot result from a primitive knowledge of the human figure nor come out of a period in which the science of anatomy is neglected" (4). It represents the idealized norm and derives from an extensive and intimate knowledge of the many individual variations which normally occur in almost all phases of anatomical structure and relationship.

Vesalius and Leonardo da Vinci are principally responsible for the initial development of these latter two more advanced forms of anatomic illustration. They blazed the trail for a rapid expansion of man's knowledge and understanding of his own body.

THE STATUS OF ANATOMICAL KNOWLEDGE AND ITS GRAPHIC ILLUSTRATION IN THE CIVILIZATIONS OF ANTIQUITY

In early civilizations the laws, customs, and prejudices which were usually an integral part of religion and philosophy, prohibited any real progress in the development of anatomical knowledge and consequently of its graphic expression. The Chinese of the Chou Dynasty (1122–249 B.C.), for example, possessed an elaborate system of anatomical canons collected in a treatise called *Nei Ching*. This consisted of an intricate hierarchy of social relationships between the several organs of the body. Philosophy and medicine were so closely combined that the practical and useful aspects of the latter were inextricably involved and lost in a vast and elaborate theoretical system. The highly schematic illustrations found in Chinese medical and anatomical treatises bear witness to this fact. Not until relatively modern times has medical science in China become free of the theoretical and traditional.

In the near eastern and early Mediterranean cultures medicine was also closely associated with philosophical and religious systems. Probably the earliest extant three-dimensional anatomical illustration of a visceral organ is a Babylonian model of a sheep's liver dating from about 2000 B.C. The liver according to the lore of ancient Babylon, was believed to be the seat of the soul, sickness to be a supernatural visitation, and seeking to ascertain the will of the gods the first step in the treatment and cure of disease. Babylonian physician-priests from about 3000 B.C. studied, therefore, the livers of sheep killed for sacrifice. The liver and models of it with prophetic inscriptions in cuneiform engraved upon them functioned to signify and record for the priests the will of the gods.

In ancient Greece, in addition to the high peak to which the sculptured representation of external human form was carried in the great period of Grecian pre-eminence, votive offerings of many visceral organs were fashioned and hung in the temples of Aesculapius. The priests of Aesculapius, the Aesclepiadae, practiced medicine as a secret and hereditary art. No texts of anatomy were necessary since secret instruction in the temples was passed on from one generation to the next by the Aesclepiadae. The votive offerings or donaria were an essential part of this cult, offerings given in gratitude for escape from disaster, in anticipation of a favor, or in appreciation for the cure of disease by the temple priests. They may have had some use in anatomical instruction within the sacred walls.

The cult of the Aesclepiadae was carried to Rome in 291 B.C. and later with little alteration into latinized Christianity and into the Middle Ages. With Hippocrates (460–377 B.C.), however, Greek Medicine began to emerge from its position of complete domination by the priests of Aesculapius. Hippocrates makes very few references in his writings to the opening and dissection of the human body ". . . and these examinations concern the investigation of the thorax and abdomen in order to determine the cause of death" (2). He, like Aristotle, in all probability, called largely on his dissections of lower animals for his knowledge of the structure and function of the human body. John Beall wrote as follows on the status of anatomical knowledge in Hippocratic times: "If anatomy had been much known to the ancients, their knowledge would not have remained a subject of speculation. We should have had evidence of it in their works; but, on the con-

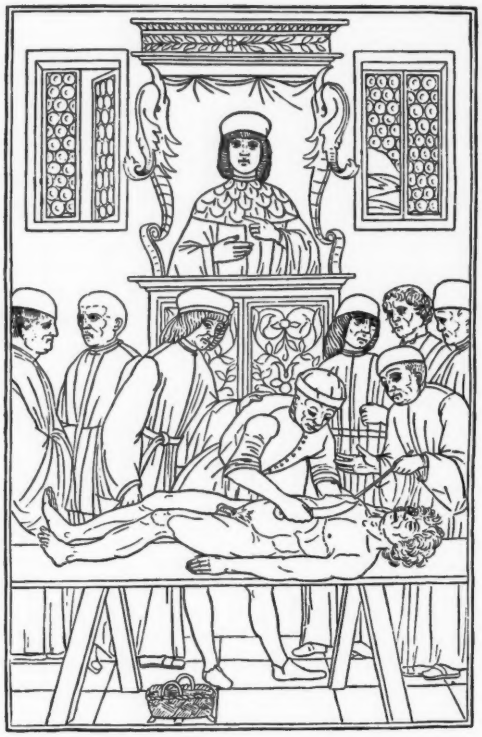

Fig. 1. Anatomical demonstration in 1493 (Joannes de Katham). (Photographed from Choulant, p. 118.)

trary, we find Hippocrates spending his time in idle prognostics, and dissecting apes, to discover the seat of the bile" (2).

It was in the University of Alexandria in the fourth century B.C. that the science of human anatomy was first studied systematically and legally. Alexandria, founded in 322 B.C. by Alexander the Great, was for several centuries the intellectual center of the known world (2). The most eminent scholars of the time gathered in its university and museum. Under the tolerant rule of the Ptolemies the anatomists, Erasistratus and Herophilus, performed human dissections and, from these, taught the science of anatomy. They made many anatomical discoveries which are still held as truths today.

Unfortunately, after the second century B.C. human dissection was no longer practiced at Alexandria. Instead of advancing, science again was allowed to regress, being gradually replaced by theorizing and discussion. The pre-eminence of Alexandrian culture declined as a result of the period of Roman domination and the capture of Alexandria later by the Arabs. The works of Erasistratus and Herophilus were destroyed. We know of them today only through the writings of Claudius Galen (201–138 B.C.), who at one time made the difficult pilgrimage to Alexandria in order to view and study a human skeleton.

To Romans in Galen's time, dissection of the human body was forbidden. This famous physician's anatomical studies, on which he based treatises which were to become unquestioned authority in the field of medicine for thirteen centuries, were, therefore, limited almost entirely to animal dissection. He made a number of important contributions to the science of anatomy but because of the restrictions imposed upon him reached some false conclusions as well.

Physicians and anatomists succeeding Galen accepted his treatises as infallible, gradually and mistakenly attributing his results to human dissection. Following the fall of the Roman Empire these treatises, along with those of other Greek and Roman physicians, were taken by the Arabs and translated into Arabic. It was the Arabs who saved for posterity what was best in ancient philosophy and science but, as in the case of Galen, not without incorporating, through translation, certain errors and misinterpretations. The Arabs were thus, for centuries, the custodians of the medical science of antiquity. They considered his texts no less infallible than had Galen's Roman successors. They contributed neither original literature nor anatomic discovery, the anatomical portions of their three great texts on medicine being compilations from Aristotle, Galen, and Oribasius. It was, in fact, contrary to the tenets of their religion to practice either human dissection or pictorial representation of the human figure.

In the Christian world the oblivion of the Dark Ages engulfed and retarded medicine just as it did all science and art. Galen and all who preceded him were forgotten, buried under the yolk of feudalism and the anathemas of the early Christian church. Personal initiative was stifled and it logically followed that this was a period in which no contributions were made to anatomical knowledge. Some Latin translations of Galen from the Arabic were eventually made in about the eleventh century by a group of Benedictine monks. Again suffering errors in translation, these were upheld as the unquestioned source of medical truth—a situation not completely overthrown until the publication of Vesalius' *Fabrica* five hundred years later.

THE RENAISSANCE OF SCIENTIFIC INQUIRY

The Arabs had established, because of their religious beliefs, a strict distinction between the fields of medicine and surgery. As learning began to emerge from the darkness of the early middle ages in the twelfth and thirteenth centuries and as the great universities began to develop in Italy, this division was maintained. Medicine was taught by respected faculties of medicine; surgery was left to barbers, bathkeepers, and public executioners. The physician felt no need for an exact knowledge of anatomy. The science of anatomy consisted almost entirely of a "reading of a translation into Latin of an imperfect summary by an Arab of Galen's teaching . . ." (13).

In the thirteenth century a change in attitude toward human dissection began to develop. In 1231 A.D. Frederich II, Emperor of Germany and King of the Two Sicilies, issued a decree ordering that at Salernum at least once in 5 years a dissection should be performed on a human body and that all physicians and surgeons of the kingdom should be present to witness it. In Venice in 1308 an annual human dissection at the medical college was authorized. These and other isolated beginnings heralded the approaching time in which anatomy was to be taught from the cadaver—at which time anatomical knowledge would be based on observed fact rather than on supposition and tradition.

Universities developed rapidly at Salernum, Venice, Florence, Bologna, and elsewhere in the fourteenth century. In these seats of learning the practice of human dissection gradually gained recognition. In the fifteenth century, in Italy, ". . . the Pope, standing in the vanguard of science, permitted dissections to be made in all Italian medical schools and paved the way for the anatomical renaissance" (2). At these early dissections, however, independent thought and observation were given little consideration. The chief interest of the professor was, instead, the verification and demonstration of the "Truths" in the accepted texts. He read anatomy from Galen or Mondino while a barber surgeon dissected the body (Fig. 1).

What was the status of anatomical illustration during this medieval period? There were in circulation for centuries an odd series of manuscripts, a set of 5 or 6 drawings with brief text, perhaps originating in an Alexandrian book no longer extant. The semisquatting figures illustrate in series the arteries, veins, muscles, nerves, and skeleton. Frequently a diagram of the reproductive organs, particularly of the pregnant woman, forms the sixth picture of the set. Professor

Fig. 2. Arterial system from a late thirteenth century Provencal manuscript in the Basel University Library. (Choulant, p. 55.)

Sudhoff of Leipzig "has been able to trace the history of this curious set of pictures in manuscript after manuscript from the middle ages down to the invention of printing" (5). These manuscripts, all of which contain an almost identical 5 or 6 picture series, have been found both in the East and in the West. It is principally this fact which leads one to believe that the pictures do stem from a common root in the late Alexandrian School, probably having been used there in the teaching of anatomy (Fig. 2).

The first man to break the bonds of tradition in anatomical study was Henri de Mondeville, who lectured at Montpellier at the end of the thirteenth century. With some dissection, illustration, and the use of a series of 13 charts on human anatomy in his teaching, he challenged and weakened the supremacy of traditional medieval anatomic art. The influence of the traditional series is found in de Mondeville's work but his contributions are in large part original.

Henri de Mondeville paved the way for his fellow student Mondino, later professor of anatomy at the University of Bologna (1303–1326) who is

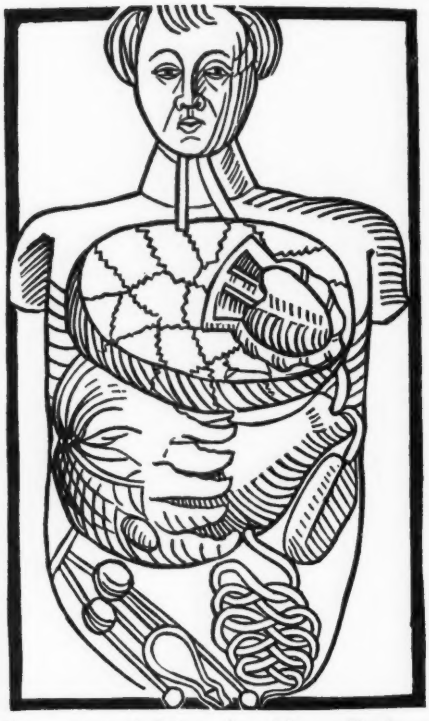

Fig. 3. Anatomical figure from Magnus Hundt, 1501 (Choulant, p. 125). Note especially the five lobed liver which, as Choulant points out, derives from an old Galenic error based on animal dissection (e.g., the pig).

commonly known as the "Restorer of Anatomy." Mondino was the first teacher in Europe known to have taught anatomy from the human cadaver. "Mondino did not revive critical investigation, nor in any way alter the intellectual methods of anatomy, but he brought back human dissection into the study of medicine" (5).

Mondino's text of anatomy, *Incipit Anathomia Mundini*, first appeared in manuscript form in 1316. Its purpose was the simplification of the teaching of anatomy for his students. For two centuries it was widely used, frequently as an introduction, or an addition, to the translated works of Galen. The original manuscript contained no illustrations though drawings were added to many of the 25 or more printed editions of Mondino which appeared between 1478 and 1580.

The anatomy of Mondino "... although not the first treatise on anatomy to be illustrated, is the natural starting point for a consideration of pre-Vesalian anatomy ... On account of the extensive use in medical schools it forms the genetic link between the ancient anatomy and that of the renaissance period. It was the forerunner of the anatomical treatises that appeared before the epoch-making book of Vesalius" (12).

The innovations of Mondino were, however, not continued. Civil and ecclesiastical authorities granted only in a few instances the right to dissect the human body. ". . . The practical study of human anatomy did not gain recognition until the sixteenth century." In fact, "... the prejudice against dissection was so great that for nearly a century after his death few men dared to repeat the acts of Mondino" (2).

PRINTED ANATOMICAL ILLUSTRATIONS FROM 1491 TO THE PUBLICATION OF THE FABRICA IN 1543

Reflecting upon the story of anatomical illustration and literature, one cannot overemphasize the importance of the invention of printing with movable type or the development of wood and metal engraving techniques for the printed reproduction of graphic material. These two great innovations of the 15th century opened previously unimagined pathways for the effective and widespread communication of facts and ideas. Important in all fields of human intelligence, they were no less vital to the birth of modern medical teaching. The texts and illustrations of ancient and medieval times were, of necessity, manuscripts—laboriously prepared and then copied by hand. Few volumes of any such manuscript could be made available for study. Printed books, by comparison, gave ideas wings and made possible their spread to large numbers of students often geographically far removed from the author and his knowledge.

To reproduce anatomical illustrations by the wood engraving process (the use of metal to replace wood was a later development) the artist or professional engraver had to transfer drawings in reverse onto a smooth wooden block and then to engrave the image by hand, cutting the wooden surface with sharp gravers or knives. This is a difficult and tedious procedure employed until relatively recently when it was replaced by modern photoengraving techniques. Hand engraving was a craft requiring the highest skill. The works of Vesalius, for example, seem the more remarkable when one realizes that the two hundred and fifty odd plates of his *Fabrica* had to be cut, one by one, in this exacting manner.

Of the printed pictorial representations of human anatomy before Vesalius, practically none were the result of actual dissection or original observation. They were, instead, based in large

part upon the earlier traditional diagrams mentioned above. "... The consideration of these crude sketches reveals to us the conditions under which scientific men worked, the mental habit of the period, the educational practice in science, and the degree to which accurate observation in anatomy prevailed" (12). In fact dissection in the fourteenth and fifteenth centuries was performed only in order to learn and to verify the works of ancient authors. Leonardo da Vinci was actually the first anatomist to dissect in order to look objectively at the true structure of the human body.

We have seen also that in medieval times the physicians felt no need for anatomic representations from nature—nor with dissection forbidden could such a need have been met. As late as the last half of the fifteenth century, even though the invention of book printing and of the wood cut had made possible the relatively extensive and rapid multiplication of illustrated books, physicians were content with the crude schematic-anatomic representation which made graphic the anatomic theorizing of the ancients. It was their desire "to represent pictorially and to put before the student what, up to that time, had been preserved only through words and memory" (4).

In the period from 1491 until the publication of the *Fabrica* in 1543, about one hundred different anatomic cuts were published excluding the seven to eight hundred prepared by Leonardo da Vinci which became lost after the latter's death and were not published until nearly five centuries later.

Of those plates actually published by the immediate successors of Mondino, the schematic illustrations of Peyligk (1499) and Hundt (1501), both of Leipzig, are worthy of note (Fig. 3). The drawings of both are diagrams, not sketches from nature. Also there was Laurentius Phryesen of Strassburg (1518) who in his medical text *Spiegel der Artzney* published two anatomical plates. The six brain anatomy figures surrounding his visceral diagram are an important innovation to the roster of early anatomical plates (Fig. 4).

The first anatomical books to contain pictures systematically illustrating the text were those of Berengario da Carpi (1521). Berengario is considered to be the first independent anatomical investigator of modern times. In his *Commentaries* he subjects both Galen and Mondino to independent critical examination for the first time. He is alleged to have based his studies on the dissection of more than one hundred human bodies. In addition, his illustrations show a distinct advance in the delineation of nature, though there remains a marked dependence upon the tradi-

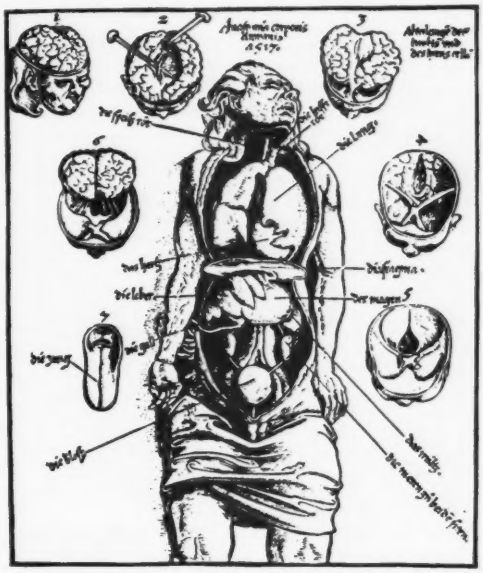

Fig. 4. Anatomical figure from Laurentius Phryesen, 1518. (Choulant, p. 131.)

tional patterns and a tendency toward plagiarism from earlier works. In spite of his short comings, Berengario marks the true beginning of the renaissance in anatomical illustration. His work stimulated a period of emphasis on "attempts at individually correct anatomic illustrations, which gradually free (d) themselves of schematic and arbitrary features . . ." (4).

John Dryander (Johann Eichmann, 1500–1560), a German physician and professor of anatomy at Marburg, was another important practical anatomist of this period. His edition of Mondino's anatomy, published in 1541, contained 45 illustrations, most of them copies of Berengario, a few showing original observation. Dryander, was one of the most impassioned opponents of the new anatomical science brought into being by Vesalius.

Leonardo da Vinci, the greatest figure in pre-Vesalian times, I have so far mentioned far too briefly. He died 18 years before the young Vesalius began his work at Padua. In his lifetime he completed a tremendous number of original dissections, notes, and magnificent red chalk illustrations on the structure and function of the human body which as anatomical illustrations have never been excelled. The project which Leonardo concieved was of tremendous scope "... a graphic anatomy of man from birth to old age in many volumes" (11). It is a tragedy that

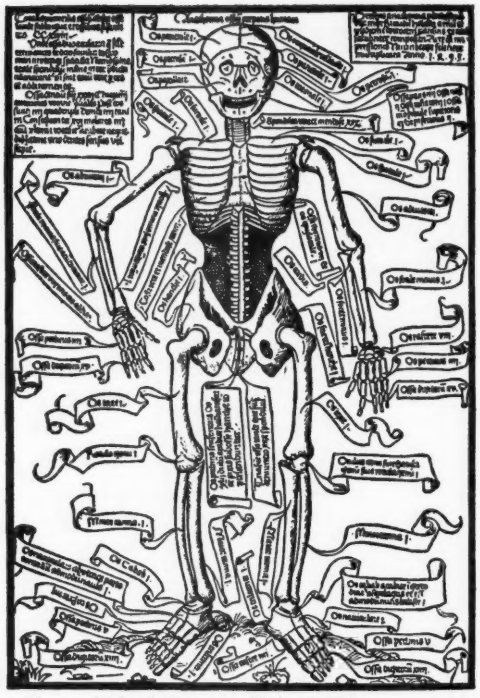

Fig. 5. Skeletal figure by Richard Helain, 1493, published as fugitive sheet. (Ball, p. 38.)

with his death in 1519 these drawings were for many centuries lost to the world. As Professor McMurrich has written comparing the contributions of Leonardo da Vinci and Vesalius to medical science and teaching: "Leonardo was the first to create a new anatomy, but he created it for himself alone; Vesalius demonstrated a new anatomy to the world. It was the publication of Vesalius' *Fabrica* that revolutionized anatomy, while Leonardo's drawings were lying unpublished. . . . We must credit Leonardo as being the forerunner of the new anatomy, but Vesalius must be recognized as its founder" (14).

THE RENAISSANCE

"This, the Revival of Learning, includes an indefinite time in European history. The seeds of the new movement were planted in the middle ages, but they bore no fruit until the time had arrived for an apparently spontaneous outburst of intelligence" (2). The Anatomical Renaissance began in Italy in the sixteenth century and passed northward and westward to Germany, Holland, England, and finally, to America.

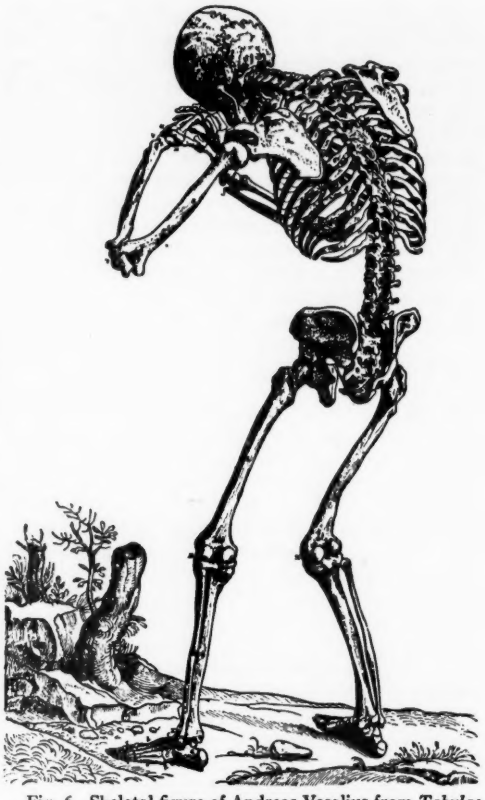

Fig. 6. Skeletal figure of Andreas Vesalius from *Tabulae Anatomicae* and *Fabrica* 1543. (Choulant, p. 179.)

A continuous stream of anatomical discoveries were made in Italy in the sixteenth century. Printing and wood engraving were further developed and early in this century a type of anatomical teaching aid known as "fugitive sheets" (*Fliegende Blätter*) was developed. These were single sheets, printed and sold separately, bearing wood cut prints of anatomical figures. These were probably hung in barber shops and baths and sold not only to medical practitioners but to a curious general public as well.

The first of these, printed in 1493 in Nurnberg, is a skeletal figure attributed to Richard Helain, a Paris physician (Fig. 5). Some of the illustrations which were printed as fugitive sheets still bore a frank resemblance to the traditional medieval series of 5 anatomical figures. The fugitive sheets, however, served a distinct teaching purpose no matter how crude they happened to be in concept or execution.

In 1538 Vesalius published a series of 6 such plates which he called his *Tabulae Anatomicae*, plates which later were incorporated into the great *Fabrica*. Unlike the earlier sheets, those of Vesalius were not intended for popular instruction. They were prepared instead as aids to true scientific study for his classes in anatomy at the University of Padua. To a degree far surpassing anything which preceded them, these plates were faithful to nature, skillfully drawn, and beautifully engraved on wood. They represented a new departure, a revolutionary concept, the birth, in fact of the modern science of anatomy and of anatomical illustration as we know it today.

CONCLUSIONS

Regarding his own *Tabulae Anatomicae* "Vesalius says that no one can learn either botany or anatomy from figures alone, but illustrations are a valuable means toward the imparting of knowledge" (2). He described as follows the habit of mind by means of which he rescued anatomy from the bonds of blind traditionalism: "I acknowledge no authority save my own eyes. I want liberty to compare the data of Galen (Prince of Physicians!) with the tangible facts of bodily structure" (18). Vesalius was the great reformer of anatomy. With the publication of the *Fabrica* he may be said to have founded the *science* of anatomy, making of it an exact study of the component parts of the human body and of their intimate relations, one to the other, as observed in the actual cadaver (Fig. 6). Through his work he achieved three important goals:

1. The elimination of anatomic prejudices by means of objective and scholarly criticism.

2. The moulding of anatomic science into a consistent whole by the addition of new and objectively observed fact.

3. The establishment for anatomical illustration of an artistically beautiful approach to the drawing of anatomic subjects from nature which was to be employed from that point on into modern times (4).

"As a light pouring into a prism attracts little notice until it emerges in iridescent hues, so it was with anatomy: after passing through the brain of Vesalius it bore rich fruit which has been gathered by many hands. To turn from the writings of Galen, Mondino, Hundt, Peyligk, Phryesen, and Berengario da Carpi to the beauties of Vesalius's *De Humani Corporis Fabrica* is like passing from darkness into sunlight. To both anatomists and artists this book was a revelation. For more than a century after its appearance the anatomists of Europe did little more than make additions to, and compose commentaries upon, the conjoint triumph of Vesalius and Van Calkar. For more than two centuries the osteologic and myologic figures of the *Fabrica* formed the basis of all treatises on Art-Anatomy" (2).

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REVIEWS OF NEW BOOKS

I HAVE greatly enjoyed Robinson's *Tom Cullen of Baltimore.*[1] It is an arresting and masterful contribution, an exquisite portrayal of the subject's hardy religious forebears, of his birth and early development in southern Canada during the family's peregrinations in the Province of Ottawa in the country which lies immediately north of Lake Ontario.

Tom Cullen's life was cast in a religious mold; his early surroundings were contributory to the protean interests with which he has been identified throughout his mature years. Rarely, if ever, do we read of a long life devoted to so many professional, personal, and civic duties, of a man so ardently and persistently determined in whatsoever he undertakes, until the work at hand is accomplished.

After his father, the Reverend Thomas Cullen, was called to a church in Toronto, young Tom, at the age of 13, took on a newspaper route. For this, he had to be awake every weekday morning at 3:30. He continued to carry papers, thereafter, until his graduation from the University of Toronto Medical School, in 1890.

During his boyhood years, Tom Cullen came to know and admire Dr. Leslie Sweetnam, subsequently his preceptor, and it was his admiration for the latter which influenced Tom to become a doctor. Dr. Sweetnam introduced him to Dr. Howard A. Kelly, who stopped en route at Toronto during one of his many trips to the Canadian lake country; and it was through intercession for him by Dr. Sweetnam, while serving as an intern in Toronto General Hospital, that Dr. Cullen was promised a place on the junior staff of Dr. Kelly at Johns Hopkins.

Thomas Cullen's life at Hopkins began before Johns Hopkins had a medical school. Two years as intern and 6 months leave for study in Europe were followed by 3 years in charge of gynecological pathology, which was probably the happiest and most productive period of his life and was coincident with the earliest years of the medical school, which opened its doors to its first freshman class in 1893.

A year as resident in gynecology followed; then came an impasse. Kelly made tentative preparation to recommend that Dr. Cullen revert to full charge of gynecological pathology; he was not inclined to create an opening in clinical gynecology. Despite his failure to secure an appointment, Cullen adroitly decided to make a future in Baltimore, in gynecology and abdominal surgery, whereupon Dr. Kelly endorsed him as associate in gynecology.

The building of a practice, growth of experience as a clinician and as a teacher and, most vital, investigation and contributions to the world literature on gynecological pathology, in which medical illustrator Max Broedel played no small part, occupied the ripening years.

Then came disagreement and confusion at Hopkins; differences of opinion regarding full-time teaching versus private practice and part-time teaching almost tore the school apart. With Kelly's gradual withdrawal and Whitridge Williams' ascendency to professor and chief of obstetrics (Cullen still an associate specializing in gynecological pathology but, in 1919, appointed to follow Kelly as head of the department of gynecology, with the title of "Professor of Clinical Gynecology"), a struggle developed to determine whether gynecology should be united with obstetrics, to become an adjunct of Williams' department, or should remain separate.

In 1919, Williams had his way. In 1923, when it came time for occupancy of the new obstetrical and gynecological building, he recanted for reasons which need not be gone into here (see page 303) and together, he and Cullen recommended to the trustees that the department of gynecology should remain separate and independent. Shortly it became independently aligned with the department of surgery.

Of course, Tom Cullen knows that he talked and wrote somewhat politically during those tense times. He stretched logic very thin in asserting so positively and vehemently that obstetrics and gynecology do not belong together and that gynecology and abdominal surgery should be integrated; that there is no doubt about it. There *is* doubt about it, just as there is doubt about the inevitable and invariable fitness of gynecology and obstetrics belonging together. True, as he says, we all realize that the successful man in obstetrics and gynecology tends to gravitate to the surgical work and regular hours if he is at all adapted to surgery, as I understand Whitridge Williams was not.

But Cullen did well in his contest with Williams. Few could withstand so well a man who was always right 105 per cent of the time. Most men were defeated before they entered into competition with Williams. He was a true student and went directly to the heart of things in every scientific problem he undertook; and he "bulled" through to a complete victory on nearly all other debatable issues. It must have been quite a gerrymandering accomplishment, even for politically astute Tom Cullen, to succeed, finally, in having Williams ask that the department of gynecology should remain independent.

To a religiously clean, upright man, ripe in years and scientifically and professionally successful in overflowing measure, we pay our respects. And this rare life loses none of its charm in the esthetic and gracefully worded tale of *Tom Cullen of Baltimore.*

ARTHUR H. CURTIS.

[1] TOM CULLEN OF BALTIMORE. By Judith Robinson. London, Toronto, New York: Geoffrey Cumberlege; Oxford University Press, 1949.

THE intention of the author of *Die Kreuzschmerzen der Frau*[1] is to aid the general practitioner who sees women suffering with low back pain.

He emphasizes the need to consider the patient as a whole rather than from the specialist's narrow point of view. At the same time he considers it important to investigate all local conditions which may cause symptoms rather than to base the diagnosis on some vague constitutional disturbance.

Consideration is given to psychic factors in low back pain. These were particularly noticeable during the postwar period when a very common syndrome was low back pain associated with amenorrhea.

The book is divided into two sections; one deals with low back pain caused by disturbance in the female pelvic organs and the other with the mechanics of the female body. The first chapter consists of a detailed description of the nerve supply of the pelvic organs and the peritoneum. The relationship of the autonomic nervous system is carefully presented. An attempt is made to describe the physiological action of pain in the pelvis and of low back pain caused by pelvic disturbance. The author quotes the work of Head and Mackenzie with regard to the possibility of lower thresholds of nerve pain. He speaks of the superficial zones of hyperesthesia and vasomotor disturbance which occur as the result of a disturbance of the pelvic organs. He demonstrates the possibility of a visceral irritation causing a stimulation which is transmitted through the cord, through the cerebrospinal pain columns and ultimately over the segmental body area where the pain is felt. He shows that irritation can also come directly from inflammation in the lumbosacral or sacroiliac joints and emphasizes the fact that the construction of the female pelvis make for greater stress at these joints. Once a reflex is set up it may be influenced by psychic disturbance, and the symptoms may persist long after the original cause has been eliminated.

Reflex symptoms may also involve other structures and this may cause a spastic constipation or a dysmenorrhea. It is pointed out that the pain along the iliohypogastric and lumboinguinal nerve supply and pain over the coccyx is often on the basis of a reflex pain with the original disturbance in the pelvis.

A common and not readily understood form of lower back pain caused by pelvic disturbance is the result of the human upright position. The pelvic organs are suspended; any disturbance in them, such as retrodisplacement or prolapse of the uterus, causes traction on the supporting muscles and suspending ligaments and may result in referred pain in the lumbar areas. Retrodisplacement of the uterus can also cause low back pain by pressure against the posterior wall. In these cases, surgical replacement of the uterus results in relief.

Low back pain may often be present in cases of endometriosis and is in the form of dysmenorrhea, which is the chief symptom of endometriosis. Frequently there is a definite psychic reaction which makes the pain more intense, but it is important to find the original organic disturbance even though the psychic element is present.

A parametritis in which the inflamed structures are adherent to the posterior abdominal wall may cause low back pain by setting up reflex muscle spasms in the pyriformis and other muscles in this area. Spastic colitis, varicosities, and tumors in the pelvis may cause low back pain.

The structural differences in the skeleton of the male and female are described with emphasis on the poorer mechanics and the liability of greater strain in the female structures. The anatomical differences that are required to permit delivery, such as flat pelvis, increased lumbar curve, separation and undue mobility of the sacroiliac joint, make for strain because of weaker mechanical structure.

The disturbances that cause lumbosacral pain are described. The importance of the pendulous abdomen is demonstrated in a series of illustrations.

The close relationship between flat foot and back strain and the alteration of the pelvic angle by high heels are brought out. There may be pain not only at the pelvic angle of the lumbosacral and sacroiliac joints but also from fatigue and pain at the muscle attachment where the irritation may be set up. Pain may be caused by back strain; prolonged sitting or standing may result in muscle soreness and stiffness and finally give rise to muscle spasm.

The author quotes Haglund on the pain caused by decompensation of the back, whether it is due to an increased load or to structural weakness or both. The structural changes which are contributing factors in decompensation of the back are sacralization, underdeveloped fifth lumbar vertebra, osteoporosis, spina bifida and spondylolisthesis.

The sacroiliac joint, the various diseases that affect it, and diseases of the pelvic bones are well described.

Martius emphasizes careful examination of the pelvis and body mechanics, aided by x-ray studies. He has found that two-thirds of the cases of backache in women are due to static decompensation and one-third to organic changes. Correction of the deformity and supportive treatment are advised.

This is a thorough treatise which is in complete accord with the prominent authorities in this field. It is based on the experience of years of practice and study and is the best work on the subject. Professor Martius is a gynecologist and his knowledge of treatment of orthopedic conditions is naturally limited, but his understanding of the problems involved is extraordinary and commendable.

EMIL D. W. HAUSER.

[1] DIE KREUZSCHMERZEN DER FRAU; IHRE DEUTUNG UND BEHANDLUNG; GYNAKOLOGISCHE ORTHOPAEDIE. By Professor Dr. Heinrich Martius. 3d ed. Stuttgart: Georg Thieme Verlag; New York: Grune & Stratton, Inc., 1947.

THE "Vittorio Putti" prize for the best work in orthopedic surgery and traumatology for the three year period covering 1945–1947 was awarded to *Hallux Valgus*[1] by Carlos Khoury.

[1] HALLUX VALGUS. By Carlos Khoury. Buenos Aires: Lopez and Etchegoyen, 1947.

The book is 219 pages in length, has an excellent bibliographic review, and is well illustrated by line drawings and photographs.

An exhaustive presentation is made of the anatomy (comparative, normal, and pathological) and of the etiology and pathology of this condition.

In the treatment the author discusses and illustrates by line drawings 32 different operations for hallux valgus. Some of these are also illustrated by preoperative and postoperative x-ray findings.

Statistical studies are presented of 126 patients with 232 cases of hallux valgus. A brief résumé of each case is presented. Only 0.8 per cent of these cases were congenital; 82.5 per cent occurred in females.

The author enumerates the indications for each of the following operations which he considers admirable when indicated: (1) Silver-Stein; (2) McBride; (3) Hueter-Mayo; (4) Lapidus; (5) Keller-Brandes; (6) Schede No. 1.

This is an excellent reference book and contains much helpful information on the subject of hallux valgus. CARLO SCUDERI.

THE author[1] with the collaboration of Dutheil and Autrand in a second edition presents a monograph on inflammatory lesions of the cervix uteri. In the chapter dealing with pathologic anatomy, glandular hyperplasia (adenomatoid) is portrayed. Leucoplacia as pictured histologically differs somewhat from the customarily accepted microscopic character of the lesion. Its precancerous nature is accepted. Basal cell hyperplasia of the squamous cell epithelium is shown without considering its possible relation to surface cancer. Acute and chronic cervicitis resulting from specific types of organisms are thoroughly described and discussed. Complications of cervicitis are listed and among them is cancer. Tissue examination even in young women is stressed in order that cancer is not overlooked. With this we are in accord. Bacteriologic and other laboratory methods are given.

In the chapter on treatment, penicillin, sufonamides, and vaccines are discussed. Hormonal therapy is considered. Local application of medicaments is described; among which are intrauterine injections. We are opposed to the latter management. Destruction of the mucosa by various types of cauterization and treatment with diathermy, ionization, high frequency currents, ultraviolet rays, radiotherapy, cervical amputation, and hysterectomy are thoroughly discussed.

For a résumé of the historical aspects and the various possible methods of treatment this book has value. The clinical use of the monograph is somewhat limited owing to the presentation of diagrammatic drawings rather than photographs.

JOHN I. BREWER.

[1]LES MÉTRITES DU COL; ÉTUDE ANATOMO-CLINIQUE NOUVEAUX TRAITEMENTE. By Pierre Durel, M.D. In collaboration with Drs. Lucien Dutheil and Hubert Autrand. 2d rev. enl. ed. Paris: Masson et Cie, 1948.

THE author of the 384 page monograph *A Surgeon's Guide to Local Anesthesia*[1] has thoroughly described his methods in the use of local anesthesia which have been developed over a period of many years of experience at the Sydney Hospital in Australia. The preparation of the patient and the gentle careful manipulations of the surgeon are stressed. The text covers the drugs employed, the manner of preparation of the solutions, and then describes the minute technique of injection by regions and operations. There are 200 figures used to illustrate the text.

The use of adrenalin in the anesthetic solution for thyroidectomy in toxic cases and in finger block anesthesia is to be condemned. It would seem wise that some warning be given those using local anesthesia that hematomas can occur when adrenalin is used unless the most meticulous hemostasis is obtained. These are minor criticisms of an otherwise excellent treatise and detract only mildly from its value.

It is to be hoped that such a monograph may stimulate more surgeons to learn to work under local anesthesia since the gentle dissections necessary serve to train the surgeon to handle tissues with greater respect in all cases. THOMAS C. DOUGLASS.

THE author of *Care of the Surgical Patient*[2] concisely states most of the important factors necessary for the excellent clinical care of the surgical patient. In discussing the entire field of surgery and allied branches, many details in treatment are either eliminated or mentioned briefly.

In the general consideration of the patient, the significance of specific symptoms and signs is stressed. Fluid and electrolyte balance, nutrition, hemorrhage, shock, and surgical infection are discussed generally, along with fundamental therapeutic principles. Regional and special surgery covers considerable territory, from the integumentary system to surgical diseases of the nervous, respiratory, cardiovascular, gastrointestinal, and genitourinary systems; finally, conditions pertaining to orthopedic, plastic, and pediatric surgery are reviewed. The usefulness of the chapters on endocrine diseases and hormone therapy is not minimized by their brevity. The material presented is basic and pointed. This is best exemplified in the remarks about hypoparathyroidism. Clinical and laboratory methods are simplified and their relative importance reviewed. The table on chemical laboratory tests alone is an important contribution for the busy clinician. This and similar tables should be extremely helpful to all of us. Reference to this section for the interpretation of most of the clinical laboratory tests will clarify many points that ordinarily lead to confusion.

[1]A SURGEON'S GUIDE TO LOCAL ANESTHESIA: A MANUAL OF SHOCKLESS SURGERY. By C. E. Corlette, M.D., Ch.M. (Syd.), F.R.A.C.S. Baltimore: The Williams & Wilkins Co., 1948.

[2]CARE OF THE SURGICAL PATIENT; INCLUDING PATHOLOGIC PHYSIOLOGY AND PRINCIPLES OF DIAGNOSIS AND TREATMENT. By Jacob Fine, M.D. Philadelphia and London: W. B. Saunders Co., 1949.

Finally, the ideas of preoperative and postoperative care, though not entirely new, are worthy of consideration. Oxygen therapy is fully presented and the tables regarding common and special drugs should not be overlooked.

This book can serve as an excellent guide to medical students, interns, and residents in the care of the surgical patient. Moreover, it should prove to be equally helpful to the busy clinical surgeon.

VINTON E. SILER.

THE book of 224 pages by Burch and Winsor entitled *A Primer of Electrocardiography*[1] is highly recommended to beginners in the study of electrocardiography. It is a primer as indicated in the title. The authors are dogmatic, as pointed out in the preface. Basic definitions are clearly made. Standard views are held. The new material on the intrinsic deflection and ventricular gradient is noteworthy but brief. The authors are concerned with electrocardiography as a science and have not detracted from the worth of the book by a vain attempt to include correlations of electrocardiographic patterns with symptomatology, physical findings, or other laboratory studies. They have included very little material on unipolar extremity limb leads.

CHAUNCEY C. MAHER.

THE fifth edition of the authoritative text *Nutrition and Diet in Health and Disease*[2] by McLester gives evidence of thorough revision, including the chapter on the feeding of infants by Dr. Philip Jeans and that on nutrition in industry by Dr. Robert S. Goodhart. A new chapter on the feeding of surgical patients has been contributed by Dr. Charles C. Lund, Harvard Medical School.

Part I deals with nutrition in health. It offers in simple and readable fashion a well organized survey of facts and principles drawn from the related fields of physiology, biochemistry and calorimetry. The soundness of the concepts presented qualifies it as a review for the practitioner of medicine while the absence of technical expressions leaves it accessible to a nonmedical public.

Part II offers a somewhat more difficult problem and perhaps a rather less satisfactory solution, in that nutrition in disease in this period of rapidly developing concepts lends itself with difficulty to summary treatment. This disadvantage is at least partially overcome by the ample bibliographies furnished with each chapter. EDITH FARNSWORTH.

THE monograph entitled *Regional Ileitis*[3] has historical as well as scientific importance. It is historical in that the author Burrill B. Crohn with Drs. Ginzburg and Oppenheimer first described this disease in 1932. These nonspecific granulomas of the ileum had been reported previously as unusual lesions but not in terms of a definite clinical entity. During the years which followed the original report, much information has accumulated. This has been condensed in a small volume which can be read in a few hours.

In addition to assembling a complete review of the literature and writing an authoritative discussion of the disease, the author has placed on record detailed analysis of his large personal series of cases. Many important facts are brought out and by way of illustration a few will be mentioned.

The many theories of the pathogenesis of the disease are discussed without conclusion. In the author's 222 cases, 90 per cent occurred in patients between the ages of 10 and 40 years and there was a slight predominance of males.

When the disease occurs in the acute form, spontaneous cure usually takes place so that surgical intervention beyond an exploratory laparotomy for differential diagnosis is contraindicated. It is essentially a chronic disease often with a long insidious onset. Diarrhea is a prominent feature. It occurred in 165 of Crohn's 222 cases. The stools never contain pus and rarely blood only 11 instances in this series. An abdominal mass was observed in 76 cases. Intestinal obstruction occurred in only 10 cases.

The frequent occurrence of "skip-lesions" and of internal and external fistulas is brought out. Fistulas in the abdominal wall occur exclusively in the scars of previous laparotomies. There were 36 instances of anterior wall fistulas in Crohn's series, all of them in appendectomy scars. Perirectal abscesses and fistulas occurred in 39 cases. Perianal fistulation may precede the other symptoms of the disease and when these fistulas are accompanied by diarrhea, ileitis or ulcerative colitis is a likely possibility. Long term remissions are not infrequent and spontaneous cures probably take place.

Acute perforation with generalized peritonitis is extremely rare, but slow perforation is a common complication. It results in internal fistulation between loops of adjacent bowel or the urinary bladder.

Gross hemorrhage from the bowel is uncommon. It occurred in only 11 of Crohn's cases.

The diagnostic value of radiographic studies is emphasized. The Kantor "string-signs" and the finding of "skipped-lesions" are essentially pathognomonic. Mucosal type distortion gives earlier but unreliable evidence.

Very few cases are cured by medical management. Resolution with this form of treatment occurred in only 12 of Crohn's cases. Sulfonomides, penicillin, and streptomycin are essentially ineffectual. Thus far, only surgery will arrest the resistant cases, but there is no unanimity of opinion regarding the best form of operative management. Dr. Crohn favors ileotransverse colostomy with transection of the ileum and supports his choice upon the record of comparative mortality and follow-up results. This type of opera-

[1] A PRIMER OF ELECTROCARDIOGRAPHY. By George E. Burch, M.D., F.A.C.P., and Travis Winsor, M.D., F.A.C.P. 2d ed. Philadelphia: Lea & Febiger, 1949.

[2] NUTRITION AND DIET IN HEALTH AND DISEASE. By James S. McLester, M.D. 5th ed. Philadelphia and London: W. B. Saunders Co., 1949.

[3] REGIONAL ILEITIS. By Burrill B. Crohn, M.D. New York: Grune & Stratton, 1949.

tion was carried out in 57 of his cases. It is generally agreed that the ileum should be transected in every sidetracking operation. Some surgeons believe that the diseased segment of the ileum should be resected either as a primary procedure or following the short-circuiting operation.

The recurrence rate following operation has varied from 10 to 30 per cent. Many of the recurrent lesions can be controlled by conservative treatment. A few require further short-circuiting procedures or resection.

Ileojejunitis and ileocolitis pose no special problems. Both are discussed and documented with illustrative case reports.

Surgeons, internists, and general practitioners, alike should find much to interest them in this book.

J. DEWEY BISGARD.

THE second edition of Ritter's book on emergency surgery,[1] which followed the first edition in relatively short time is welcomed since it contains additional valuable material gathered in the meantime and during World War II. The book accumulates the experience of the author's surgical training under Professors Sauerbruch andClairmont, and as director of a large surgical department. The title would be somewhat misleading were it not for the explanatory subtitle. The author not only deals with surgical measures which must be done immediately, but also with delayed surgical emergency procedures in which the time factor is not dominant. The main topic deals with surgical technique. A summarization of surgical emergency procedures alone, however, would be definitely one-sided and make the book inferior. The author was aware of that and included a short discussion of the physiological and pathologic physiological disturbances causing or following the emergency and measures to combat them. Limitation of space, unfortunately, seemed not to have permitted a more generous discussion.

The book is divided in a general and special section. In the general section, aside from preparation of instruments and a discussion of various anesthetic agents and their administration, such important subjects as shock, collapse, transfusion of blood and blood substitutes are discussed. A general outline of the treatment of burns, wounds, infections, injuries to the vessels and nerves, is followed in the special section by a detailed application of these measures to the various parts of the body. To mention a few, the section on the head, chest, and neck is excellently described, particularly the chapter on gunshot injuries. Emergency surgery pertaining to the chest and thorax is masterfully treated. The influence of the teachings of the author's former chief, Sauerbruch, is undeniable. The chapter on the abdomen deals with the description of the whole gamut of recognized surgical technique. In this chapter a more detailed description of the preoperative preparation of the patient (decompensation treatment of the ileum, etc.) would be welcome. The chapter dealing with the emergency treatment of injuries and infections of the urogenital system, of spine and spinal column, is concise. The chapter on the extremities is particularly well done. However, a more detailed description of the general plastic and reconstructive procedures would add to the quality of this section.

The text is concise, is clear, and profusely illustrated. The book is the mature consideration of an experienced surgeon and highly to be recommended. In spite of economic handicaps and restrictions, paper quality, printing, and binding are good, a credit to the reputation of the publisher.

HANS MAY.

[1]NEUE DEUTSCHE CHIRURGIE. (P. v. Bruns.) 63d vol. NOTFALLCHIRURGIE, DIE AUSFUEHRUNG DER DRINGLICHEN BLUTIGEN EINGRIFFE. By Adolf Ritter, M.D. 2d rev. enl. ed. Stuttgart: Ferdinand Enke, 1949.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

CLINICAL PATHOLOGY; APPLICATION AND INTERPRETATION. By Benjamin B. Wells, M.D., Ph.D. Philadelphia and London: W. B. Saunders Co., 1950.

STILLBIRTHS; THEIR EPIDEMIOLOGY AND SOCIAL SIGNIFICANCE. By Ian Suterland, M.A.(Cantab.), D.Phil. (Oxon.), F.S.S. New York, London and Toronto: Geoffrey Cumberlege, Oxford University Press, 1949.

LA CRANIECTOMÍA A TRAVÉS DE LOS SIGLOS. By Rafael Vara López. Valladolid, Spain, 1949.

HORMONES IN CLINICAL PRACTICE. By H. E. Neiburgs, M.D. New York, London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1950.

ÚLCERAS DE LAS EXTREMIDADES INFERIORES DE ORIGEN VASCULAR. By P. Piulachs. Barcelona: Salvat, 1949.

PROCEEDINGS OF THE FIRST NATIONAL CANCER CONFERENCE. New York: American Cancer Society and The National Cancer Institute of the U.S. Public Health Service, Federal Security Agency, 1949.

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE; A TEXT IN APPLIED PHYSIOLOGY. By Charles Herbert Best, C.B.E., M.A., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada), and Norman Burke Taylor, V.D., M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.) 5th ed. Baltimore: The Williams & Wilkins Co., 1950.

UROLOGIC ROENTGENOLOGY. By Miley B. Wesson, M.D. 3d rev. ed. Philadelphia: Lea & Febiger, 1950.

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